Cost-Effectiveness of Venetoclax in Combination with Obinutuzumab in First Line Chronic Lymphocytic Leukemia in Colombia

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PRESENTED AT:

INTRODUCTION

World Health Organization has defined chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL / SLL) as a neoplasm composed of small monomorphic mature B cells that express CD5 and CD23 (1). Since the initial description of the Rai (2) and Binet (3) staging systems more than four decades ago, there have been tremendous advances in understanding the prognostic factors that predict OS timing. CLL is the most common adult leukemia in Western countries. The annual incidence rate is approximately 5 cases per 100,000 people and increases dramatically with age, to > 20 cases per 100,000 people over 70 years of age. This means that approximately 2 500 new cases occur in Colombia each year. As the life expectancy of the population increases, the incidence of the disease is expected to increase as well.

The current treatment options for front line patients diagnosed with CLL vary based on age and any comorbidities they may have. Patients who have certain chromosomal abnormalities such as del17p/TP53 are known to experience reduced treatment efficacy compared with patients without these genetic abnormalities. The current treatment options for del17p/TP53 patients include Ibrutinib, chlorambucil + obinutuzumab, or Venetoclax (4). Al-Sawaf O et al demonstrated efficacy and safety of Venetoclax + obinituzumab (Ven+O) in CLL as the first line of treatment in patients, observing a estimated 48-months progression free survival (PFS) rate of 74 % after median observation time of 52.4 months, compared to 35,4 % in patients receiving chlorambucil + obinituzumab (5).

The objective of this study is to estimate the cost-effectiveness of Venetoclax in combination with Obinutuzumab (Ven+O) for the treatment of first-line Chronic Lymphocytic Leukemia (CLL) patients from the perspective of the Colombian Healthcare System.

METHODS

Target population: All 1st line CLL, which comprises of the entire untreated CLL population who require treatment which includes both unfit CLL and fit CLL patients (split by del17p/TP53 mutation status).

Study perspective: From a social perspective, CLL mainly affects individuals over 62 years of age, which is retirement age in Colombia, so the model does not include costs of lost productivity. Treatment of malignant diseases in Colombia is exempt from co-payments, so all costs are direct.

Comparators: Venetoclax + obinutuzumab (Ven+O), chlorambucil+obinutuzumab (Clb+O) fludarabine, cyclophosphamide, and rituximab (FCR), bendamustine+rituximab (B+R) and ibritunib.

Time horizon: Seven years.

Discount rate: 5 % for both costs and benefits.

Health outcomes: PFS and post-progression survival (PPS). Effectiveness of Ven+O vs Chlorambucil+O (Clb+O) was based on the CLL14 clinical trial (4). Relative efficacy vs FCR, BR and Ibrutinib was estimated using a network meta-analysis (6). Adverse events (EA) and utilities were taken from published studies (7).

Estimating resources and costs: Cost of venetoclax, obinutuzumab and chlorambucil were taken from Drug Price Information System (SISMED, by its acronym in Spanish) reported in the third quarter of 2020. Cost of ibritunib was taken from Circular 10/2020 (a rule that regulates medicines price in the country). Costs of applying chemotherapy, laboratory and imaging tests and doctor visits were taken from the SOAT 2020 Manual (a health tariff manual used in the country). Costs of terminal care were taken from a study that estimated healthcare costs during the last year of life in patients who die from cancer, which was done by National Cancer Institute of Colombia in 2018 (8). These costs were adjusted at 2020 prices based on the 2018 and 2019 consumer price index determined by country's central bank (Banco de la República). Cost of adverse events were taken from a study that evaluated adverse events in the treatment of patients with myeloma, which are similar (9). Healthcare resources use (CLL treatment, routine care, and monitoring, EAs, and disease progression and end-of-life care) was estimated based on the guideline proposed by NCCN and validated by two Colombian clinical experts. The results were tested using deterministic and probabilistic sensitivity analysis.

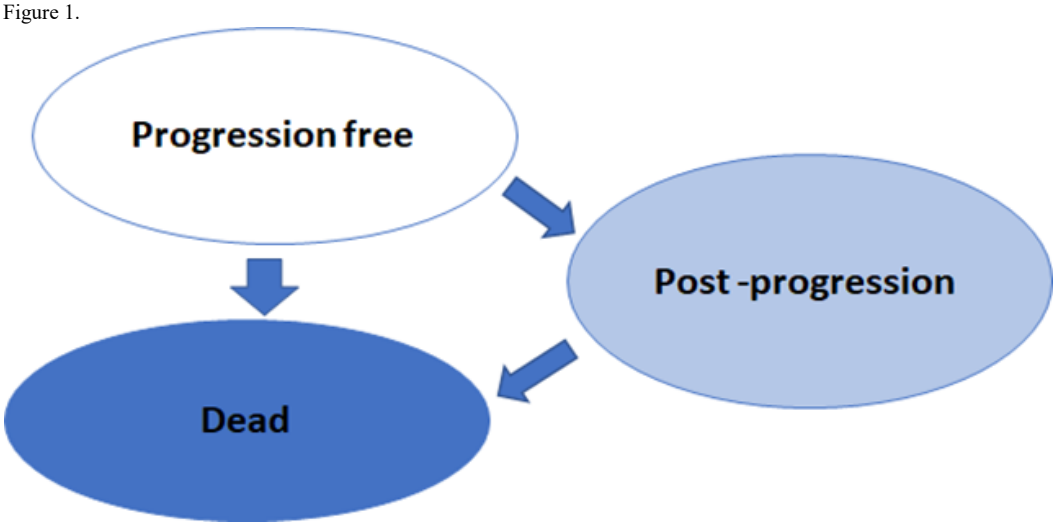
METHODS (CONTINUED)

Currency, price data, and conversion: Costs were calculated in Colombian pesos (COP) and converted into American dollars (USD), with an exchange rate of COP $ 3,693 for USD $ 1.

Choice of model: Within the partitioned survival model approach, patient pathway is split into PFS, post-progression survival (PPS) and dead and thus aligned with the CLL14 trial (4). To estimate the number of patients who belong to each of these pathways over time, an area under curve analysis has been performed. A three-state partitioned survival model has been developed (Figure 1). The three states are PFS, PPS, and Dead. Progression-free health state covers alive patients who do not progress. The post-progression health state includes patients who have progressed but remain alive. Dead health state is dictated by overall survival curve which accounts for the number of patients who have died from either CLL (using the CLL14 OS curve) or other causes (using the age and sex adjusted life tables of Colombia). The patient population distributions within each health state over time are approximated using extrapolated survival curves.

METHODS (CONTINUED)

Figure 1.



Assumptions of the model:

•Mid-cycle correction is applied to approximate costs and QALYs in every cycle. It is assumed that this approach sufficiently corrects for the fact that drug administrations are done at day 1 of each cycle, while mid-cycle correction assumes it happens mid-cycle (with less patients on treatment).

•One-off disease progression costs are calculated by assessing the proportion of patients that enter progression and death health state per cycle. This is done as it is assumed that all patients who progress, plus the patients who die, have experienced progression, and therefore progression costs apply. This may not be completely correct, as patients can die because of background mortality and because of the disease (from PFS, PP). However, how many patients die from each health state cannot be determined in a partitioned survival model.

•Treatment-specific health state utilities are assumed to account for treatment-specific adverse events. Hence, QALY losses due to adverse events are not considered when applying treatment-specific utilities. Adverse event costs are still accounted for.

•Both costs and QALY losses due to adverse events are incurred in the first model cycle.

•DuBois formula for body-surface area measurement is used to measure body-surface area.

•PFS and OS curves are constraint by background mortality hazards.

Analytic methods:

A survival analysis was used to estimate clinical outcomes probabilities in every clinical pathway. Survival analysis allows to identify these changes and determine population at risk in each cycle.

RESULTS

Total drug-related costs were, for Ven+O, $205.856.528; Clb+O, $43.695.102; ibrutinib, $711.760.070. Total disease management costs were, for Ven+O, $11.267.983; Clb+O, $11.736.309; ibrutinib, $11.363.741. Subsequent treatment costs were, for VEN+O, $33.696.782; Clb+O, $230.913.374; ibrutinib, $369.935.165. Other cost, as terminal care and AEs were, for Ven+O, $27.058.230; Clb+O, $26.242.685; ibrutinib, $22.265.075. Total discounted costs were, for Ven+O, $277.879.523; Clb+O, $312.587.469; ibrutinib, $1.115.324.050. Total discounted QALYs were, for Ven+O, 3.47; Clb+O, 3.35; ibrutinib, 3.34. VEN+O was dominant versus Clb+O and versus ibrutinib; also, was dominant vs FCR (ΔQALY's: 0.45; ΔCosts: $-201.845.667) and B+R (QALY's: 0.40; ΔCosts: $-315.606.631) Base case results are robust and consistent according the sensitivity analysis.

Baseline characteristics

PFS and OS curves were estimated using the patient level data from the CLL14 trial (4). Baseline characteristics for patients in the trial are presented in Table 1. Patients with a safety run in flag were excluded from PFS and OS analyses.

RESULTS (CONTINUED)

Table 1. Baseline features of patients in CLL14 trial (4)

Characteristic		VenO (n=216)	OClb (n=216)
Age	Median, years (IQR)	72 (67–77)	71 (66–77)
	≥75 years, n (%)	72 (33)	78 (36)
Male, n (%)		146 (68)	143 (66)
Median time from diagnosis, months (IQR)		31.2 (11.6–63.0)	29.2 (7.7–57.5)
Binet stage, n (%)	A	46 (21)	44 (20)
	B	76 (35)	80 (37)
	C	94 (44)	92 (43)
TLS risk category, n (%)	Low	29 (14)	26 (12)
	Intermediate	139 (64)	147 (68)
	High	48 (22)	43 (20)
Total CIRS score	Median (IQR)	9 (7–11)	8 (7–10)
	>6, n (%)	186 (86)	177 (82)
Estimated CrCl*	Median, mL/min (IQR)	65.2 (52.6–82.3)	67.4 (52.8–82.3)
	<70 mL/min, n/N (%)	129/215 (60)	119/213 (56)
del(17p), n/N (%)		17/210 (8)	14/208 (7)
Other cytogenetic subgroups as per hierarchy, n/N (%)	del(11q)	36/210 (17)	38/208 (18)
	Trisomy in 12	36/210 (17)	40/208 (19)
	No abnormality	50/210 (24)	42/208 (20)
	del(13q) alone	71/210 (34)	74/208 (36)
TP53 mutation status, n/N (%)	Mutated	23/216 (10.6)	19/216 (8.8)
	Unmutated	188/216 (87.0)	191/216 (88.4)
TP53 deleted and/or mutated, n/N (%)*		25/209 (12)	24/208 (12)
IGHV mutation status, n/N (%)*	Mutated	76/200 (38)	83/208 (40)
	Unmutated	121/200 (61)	123/208 (59)
	Not evaluable	3/200 (1)	2/208 (1)

Deterministic results

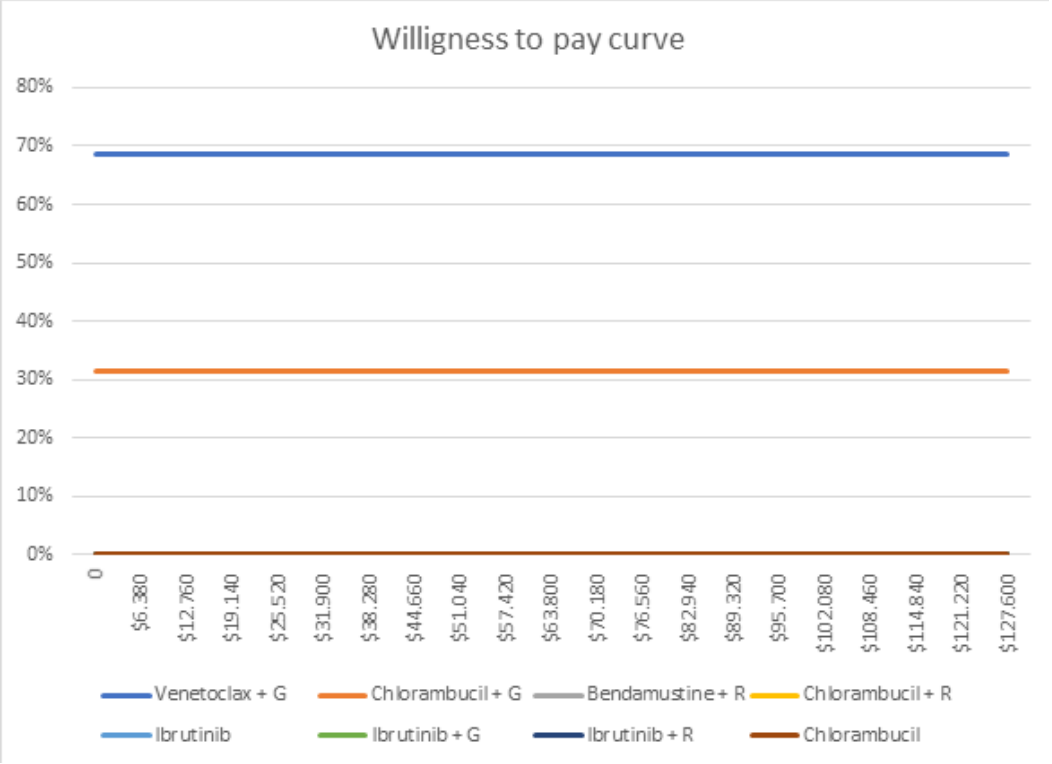
Table 2 shows the discounted total QALYs and discounted total costs, which are made up of drug-related costs, total disease management costs, and subsequent treatment costs (adverse events and end-of-life costs). These results indicate that Ven + G is a cost-saving strategy compared to all the other strategies available in Colombia for CLL treatment.

	Ven+G	Clb+G	FCR	B+R	Ibrutinib
Total drug-related costs	$ 55.742	$ 11.789	$ 10.181	$ 53.881	$ 200.241
Total disease management	$ 3.052	$ 3.178	$ 2.962	$ 3.131	$ 3.100
Subsequent treatment	$ 10.518	$ 61.471	$ 106.947	$ 125.384	$ 60.074
Other costs (adverse events)	$ 6.801	$ 6.580	$ 6.335	$ 6.869	$ 6.007
Total discounted costs	$ 76.113	$ 83.017	$ 126.425	$ 189.265	$ 269.422
Total discounted QALYs	4,13	3,92	3,67	3,73	3,98

Ven+G: venetoclax + obinutuzumab; Clb+G: chlorambucil + obinutuzumab; FCR: fludarabine, cyclophosphamide, and rituximab; B+R: bendamustine + rituximab, I+G: ibrutinib + obinutuzumab.

Probabilistic results

With a willingness to pay of $ 6,380 (1 gros domestic product per capita), VEN+G has a probability of 69 % to be the best strategy as first line in LCC in Colombia.


Willigness to pay curve
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
$6.380
$12.760
$19.140
$25.520
$31.900
$38.280
$44.660
$51.040
$57.420
$63.800
$70.180
$76.560
$82.940
$89.320
$95.700
$102.080
$108.460
$114.840
$121.220
$127.600
Venetoclax + G
Chlorambucil + G
Bendamustine + R
Chlorambucil + R
Ibrutinib
Ibrutinib + G
Ibrutinib + R
Chlorambucil

CONCLUSIONS

Analysis suggests that Ven+O is a cost-effective treatment for patients with 1L CLL and can be considered as a standard treatment option in Colombian Healthcare System.

VEN+G is dominant strategy vs all comparators available in Colombia as first line in LCC in Colombia, because patients have more OS and PFS as well as QALYs. In the same way, VEN+G saves money vs any treatment strategy, including chlorambucil. This happens because VEN+G is the therapeutic option with the lowest cost in subsequent treatments. Main strength of this decision model is that is developed through a partitional survival analysis, in which patients probability distribution in PFS and OS functions is determined, without requiring structural assumptions in the model

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DISCLOSURES

Ordoñez J. has not mentioned conflict of interest

Perdomo H. is an AbbVie employee (Value Proposition Manager LATAM North Region)

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