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Cost-Effectiveness of Idelalisib-Rituximab for the Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia

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Research Article

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Abstract

Background: A significant survival prolongation was recently reported by adding idelalisib to rituximab (IR) compared with rituximab (R) in the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL). No direct data are available about the relative safety and effectiveness of IR versus other commonly used treatments. The economic impact of novel treatments for CLL is still unknown and no study ever attempted in assessing the benefit-for-cost of IR as compared with the other available treatment options.

Aim: To investigate the economic and clinical impact of IR in CLL

Objective: To understand the potential clinical and economic advantage of IR in CLL patients who failed one prior treatment line (i.e. refractory to or relapsed after prior treatment lines), as compared with immunotherapy and chemoimmunotherapy.

Methods: A treatment-sequence model was developed to estimate the incremental cost per QALY of IR versus R, bendamustine-rituximab (BR) and fludarabine cyclophosphamide-rituximab (FCR) in the second-line treatment setting (i.e. refractory to or relapsed after first-line therapy) in Italy. Tree Age software was used to simulate second-to-third line treatment sequences by a five-states Markov model: the model was run at monthly steps for 30 years. Probabilities of progression were obtained from published randomized and phase II studies (Furman, et al. 2014, Awan, et al. 2014, Fisher, et al. 2011): data were adapted to a second-line setting according to a fixed hazard ratio of 1.4 between subsequent lines. The analysis was performed in the perspective of the Italian national health-care system.

Results: Base case analysis reported that IR improved quality-adjusted life expectancy by 1.91, 1.41 and 0.86 years as compared with R, BR and FCR. The incremental cost per quality-adjusted year (QALY) was €2,993, €16,045 and

€28,045, respectively. The main drivers of the model were: time horizon, idelalisib unit cost and treatment duration. Deterministic and probabilistic sensitivity analyses showed that treatment with IR was cost-effective at conventional willingness-to-pay threshold (€40,000 per QALY).

Conclusion: Based in this model, IR is a cost-effective option for CLL patients who deserve a second-line treatment.

Keywords: Cost-effectiveness; Chronic lymphocytic leukemia; Idelalisib; Rituximab; Bendamustine; Markov tree

Abbreviations: CLL: Chronic Lymphocytic Leukemia; IR: Rituximab; RR: Refractory; BR: Bendamustine-Rituximab; FCR: Fludarabine-Cyclophosphamide-Rituximab; PFS: Progression-Free Survival;

Background

B-cell chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries with a reported prevalence of 27 cases per 100,000 inhabitants [1] and a median age at diagnosis of 68 years in Southern Europe [2] . Patients receiving therapy can now expect disease-free intervals of around 2 years after first-line treatment [3-5], however, recurrence is still the rule. Furthermore, CLL has frequently become refractory to conventional chemotherapy. All these factors combined make it difficult to choose a safe and successful second-line treatment choice.

Idelalisib is an oral selective inhibitor of phosphatidylinositol 3-kinases delta isoform recently approved, in combination with Rituximab (IR), for CLL patients with a relapsed or refractory disease (R/R) [6] and naïve patients carrying 17p deletion or TP53 mutations. Current guidelines and expert consensus recommend IR as a suitable therapeutic option in the second-line setting [7,8]. In this subset of patients other therapeutic options are also recommended and approved in Italy so far as June 2015, such as bendamustine-rituximab (BR) and fludarabine-cyclophosphamide-rituximab (FCR). However, the above therapeutic options have not been compared in head-to-head studies while indirect comparisons with network meta-analyses [9] might be biased by heterogeneous patient selection. Moreover, the relative cost-effectiveness of IR as compared with the several available treatment options has never been attempted. Therefore, we aimed at estimating the incremental costs and benefits of IR as compared with the commonly prescribed treatments for R/R CLL in the perspective of the Italian HealthCare System. The objective of our study was to inform physicians and decision makers of the incremental costs and quality-adjusted life years of this first-in-class drugby adopting “solid” comparator treatments, including chemoimmunotherapy, and full treatment strategies, that is second-and-third line therapy sequences planned to build a decision model for tracking different treatment sequences including IR in either as a second or a third-line treatment. While the national agencies were evaluating the value for money of this new technology, we used a treatment sequence Markov model to estimate, from the perspective of the Italian HealthCare System, the cumulative health benefits and costs of second to third-line treatment sequences including IR as compared with other commonly prescribed treatments for R/R CLL.

Methods

Analytical Framework

A decision-analytic model was developed with TreeAgePro™ 2015. The model was based on a Markov model framing the natural flow of patients through 5 mutually exclusive health states (Figure 1): (i) progression-free On treatment, (ii) progression-free On extended therapy (idelalisib only), (iii) progression-free Off treatment, (iv) Progression (3rd line therapy), (v) Death. Patients could “move” monthly from one health-state to another, (i.e. cycle, according to input transition probabilities). All patients enter the model in the state “Progression-free On treatment” and receive second-line treatment with one of the four alternative therapies (IR, R, FCR, BR). Patients receiving second-line treatment with IR and not experiencing disease progression during the first 6 months move to the state “Progression-free On extended treatment”. Patients receiving second-line treatment with R, FCR or BR and not experiencing disease progression during treatment move to “Progression-free Off treatment”. It was assumed that patients progressing after 2nd line treatment with IR would possibly start a 3rd line active treatment with the standard therapy being compared with IR. Similarly, patients progressing after 2nd line treatment with standard therapy would possibly cross-over to IR at progression (Figure 2). Patients progressing during or after 3rd line treatment were assigned to palliative sub-continuous chlorambucil.

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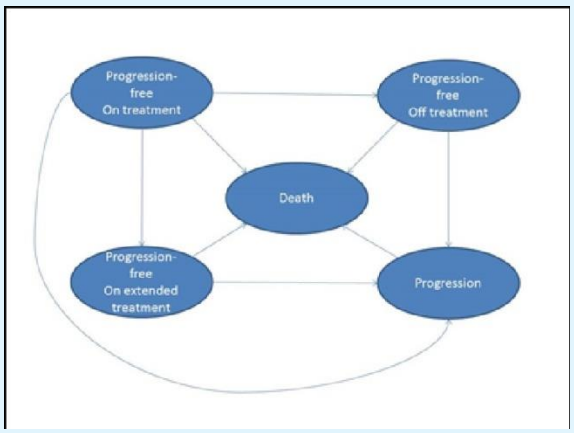

Figure 1: Markov health states.

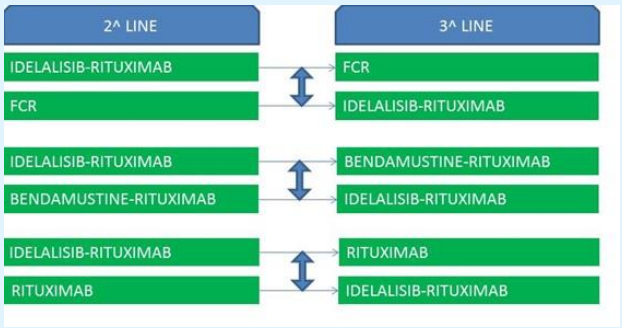

Figure 2: Compared treatment strategies. Pair wise comparisons between second-third line treatment pairs are shown.

Treatments

Patients were assigned to treatment with IR or one of 3 comparator therapies: R, BR, FCR.

The modeled treatment regimens, according to the trial reports, were:

a. IR: Idelalisib 150 mg bid plus intravenous rituximab 375 mg/m2 followed by rituximab 500 mg/m2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions [6].
b. R: intravenous rituximab 375 mg/m2 followed by rituximab 500 mg/m2 every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions [6].
c. FCR: six 28-day cycles including intravenous fludarabine 25 mg/m2 daily for 3 days, intravenous cyclophosphamide 250 mg/m2 daily for 3 days, rituximab 500 mg/m2 on day 1 (except for the 1st cycle during which rituximab dose was split to 50 mg/m2 on day 1plus 450 mg/ m2 on day 3) [10].
d. BR: six 28-day cycles including bendamustine 70 mg/ m2 on days 1 and 2 and intravenous rituximab 500 mg/m2 on day 1 (except for the 1st cycle for which a 375 mg/m2 dose is used) [11].

Progression-Free and Overall Survival

We retrieved through PubMed all the randomized studies published in the last 5 years (up to march 2016) reporting progression-free survival (PFS) and a detailed description of the frequency of adverse events for R/R CLL patients treated with IR, R, FCR or BR. Phase 2 studies were retrieved if no randomized study addressed the target treatment and setting. We therefore derived data from 2 randomized studies enrolling patients with a median of 3 [6,12], and 1 [10] previous treatment lines and from one phase II study [11] enrolling patients with a median of 2 previous treatments. We aimed at comparing the selected treatments in patient's candidates for 2nd line therapy, however, the median number of prior treatment lines in the selected studies was heterogeneous. Therefore, we adopted the hazard ratio of progression according to the treatment line as reported by a large population-based study in the Netherlands [13] and from a randomized trial [14]: a hazard ratio of 1.4 per each further treatment line after the second was therefore used and the resulting transition probabilities are reported in Table 1.

Probabilities	Data	Value	Standrd Deviation	Source
Progression-free◊Progression				
-- IR 1-8 mo	0.020 (4rd line)	0.009	0.005	[6,12]
-- IR >8 mo	0.034 (4rd line)	0.015	0.005	[6,12]
-- R	0.090 (4rd line)	0.039	0.01	[6,12]
-- RB	0.042 (3rd line)	0.028	0.005	[11]
-- FCR	0.030 (3rd line)	0.02	0.005	[10]
Treatment-related mortality		0.005	0.001	[10,11]
General mortality		0.0033	0.0001	[15]
Mortality after progression		0.045	0.005	[13,14]

Table 1: Input probabilities: per cycle probability is reported. Beta distributions for all the probabilities were estimated based on the mean value and the standard deviation reported.

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Treatment-related mortality was adopted from two studies enrolling patients with 1 or 2 previous treatment lines [10,11] and was assumed to be the same for all the compared treatments. Mortality after progression was 0.045 per cycle [13,14].

General mortality was derived from Italian 2013 life tables [15]. The weighted average life expectancy of the modelled target population, i.e. 68 year old with a male to female ratio of 1.8 [6,10,11], was calculated to be 18.25 years: monthly probability of death was estimated according to an exponential model.

Adverse Events

The model considered only febrile neutropenia and the most relevant and specific grade 3-4 adverse events: neutropenia, thrombocythopenia, anemia, diarrohea. The frequencies of adverse events were applied directly from original studies without any adjustment for the median number of previous treatment lines (Table 2). The overall rate of adverse event was equally distributed among treatment cycles, assuming that the whole treatment regimen was completed.

Event	IR	BR	FCR	R	Cost
Febrile neutropenia	30%	13%	12%	22%	2,956
Grade 3-4 neutropenia wo fever	4%	10%	59%	0%	510
Grade 3-4 thrombocythopenia	10%	28%	15%	16%	1,994
Grade 3-4 anemia	4%	17%	15%	14%	1,322
Grade 3-4 diarrohea	4%	0%	0%	0%	416

Table 2: Rates [6,10,11] and unit costs [18] of modelled adverse events.

Costs

The base-case analysis was conducted from the perspective of the national Italian health care system. Costs for drugs, intravenous administration, hospitalisations, out patients resources and management of adverse events were considered. Ex-factory prices for the year 2015 were used for rituximab and idelalisib (Table 3). Since fludarabine, cyclofosphamide and bendamustine, in Italy, are not reimbursed to hospitals on top of day-hospital tariffs, their cost was not considered in the simulation, as already captured by drug administration costs. We assumed that drug dose was always approximated to the next whole vial dose and no waste occurred. Mean charge for intravenous drugs administration was assigned the cost estimated by a large retrospective study conducted in 19 Italian hematology units [16]. The consumption pattern of outpatient resources (visits, medication, diagnostic exams, etc) was based on expert opinion of the clinicians participating in this analysis and was valued at national tariffs [17].

The costs for management of adverse events were derived from an Italian study [18] (Table 2). The cost of 3rd line therapy was calculated based on the portion of patients assigned to IR, R, BR, FCR or chlorambucil. In order to estimate cost of 3rd line idelalisib therapy, we needed to estimate the duration of idelalisib therapy in this setting, therefore we ran the model for a 3rd line setting simulation and calculated that it was 18 months.

Unit	Cost (€)	Standard Deviation	Source
Idelalisib 150 mg (1 tablet)	66,67[a]	10	[17]
Rituximab 100 mg (1 vial)	277,00[a]	50	[17]
Administration of ev drugs	288,00	50	[16]
Number of intravenous drug administrations in day hospital setting			[6,10,11]
n R			
n BR	8		
n IR	13		
n FCR	8		
	18		

[a]Ex-factory price (VAT excluded)

Table 3: Therapy costs.

Utilities

Utilities for disease-related health states and tolls for adverse events were derived from a high-quality study conducted in the UK applying standard-gamble interviews [19] (Table 4). Utility for patients on 2nd line therapy was assumed to equal those of progression-free patients, except decrements due to adverse events (pneumonia, diarrohea, anemia).

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Health state	Utility	Temporary Disutility
Progression-free	0.84	
Progressed disease	0.65	
Febrile neutropenia		-0.2
Diarrohea		-0.08
Anemia		-0.09

Table 4: Heath state utilities [19].

Distributions

Beta-distributions represented uncertainty for probabilities, rates and utilities, while gamma distributions were used for costs.

Time horizon and discount rate: A time horizon of 360 months (30 years) was chosen for base-case analysis. A yearly discount rate of 3% was used for both costs and benefits earned in the future, to calculate their present value [20].

Analysis

According to the quality standards for cost-effectiveness analyses [12], we ran a baseline analysis and calculated incremental costs, incremental quality-adjusted life years (QALYs) and the ratio between the two, i.e. incremental cost-effectiveness ratio (ICER). We also conducted first-order sensitivity analyses for all the input variables. Finally, a Monte-Carlo analysis (200 samples, 500 trials) was run and acceptability curves were plotted.

The analysis was run through TreeAge Pro 2015 ™.

Results

Base-case analysis

The results of the model show that patients' expected life expectancy ranged from 3.09 to 5.34 life years and from 2.31 to 4.22QALYs depending on the strategy being considered (Table 5). Second line treatment with IR was estimated to prolong life expectancy by 1.01-2.25 life years per patient and to improve outcomes by 0.86-1.91 QALYs per patient, as compared with second-line treatment with FCR or R, respectively.

The cumulative discounted lifetime health-care costs ranged from €113,482 to €139,281. The incremental cost per QALY-gained with second-line IR treatment was €2,993, €16,045 and €28,045 compared with second-line treatment with R, BR and FCR, respectively.

Therapeutic strategy	Undiscounted life years per patient	Quality-adjusted life years (QALYs) per patient	Lifetime Costs per patient (€)	Incremental QALYs per patient	Incremental costs per patient (€)	Incremental cost-utility ratio (€)
FCR→IR	4.33	3.36	113,482			
IR→FCR	5.34	4.22	137,561	0.86	24,079	28,045
BR→ IR	3.68	2.81	116,657			
IR→ BR	5.34	4.22	139,281	1.41	22,623	16,045
R→IR	3.09	2.31	131,299			
IR→ R	5.34	4.22	137,016	1.91	5,717	2,993

Table 5: Baseline analysis.

Sensitivity Analysis

Several one-way sensitivity analyses were run, the most relevant ones being reported in Table 6 and Table 7. The ICER was not sensitive to quality of life adjusting factors, to a reasonable variation of costs related to adverse events and to discounting. The ICER was not sensitive to patients' age, for ranges between 58 and 78 years. Even survival after progression did not influence the relative cost-effectiveness of IR versus the comparators. Rather, the ICER was sensitive, as expected, to variations of idelalisib unit cost and time horizon, being the ratio more favorable in the long-term run rather than in a short time frame. The results were also sensitive to the duration of idelalisib treatment, which is shorter than PFS, but is a very context-dependent variable, which should be assessed also outside clinical trials. The ICER was also sensitive to relevant variations of the proportion of patients being treated with IR at cross-over, i.e. third-line. The acceptability curve of IR versus FCR and BR (Figure 3) showed that the ICER was lower than the accepted Italian threshold of €40,000/QALY in 67% and 97% of the simulations, respectively [20].

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	Range		ICER (€/QALY gained)		Baseline (€/QALY)
Parameter	Lower	Upper	Lower	Upper	
Idelalisib unit cost	-30%	+30%	-1,201	33,290	16,045
Time horizon	60 months	360 months	46,989	16,045	16,045
Median duration of idelalisib treatment (after cross-over)	10 months	30 months	21,323	209	16,045
Cross-over portion	40%	60%	18,574	3,515	16,045
Febrile neutropenia IR	12%	30%	15,714	16,045	16,045
General mortality	0.0025/month	0.007/month	15,146	16,193	16,045
Mortality after progression	0.03/month	0.06/month	15,382	16,716	16,045

Table 6: Ranges for parameters and effect on ICER for one-way sensitivity analysis. IR versus BR.

	Range		ICER (€/QALY gained)		Baseline (€/QALY)
Parameter	Lower	Upper	Lower	Upper	
Idelalasib unit cost	-30%	30%	-585	56,674	28,045
Time horizon	60 months	360 months	109,624	28,045	28,045
Median duration of idelalisib treatment (after cross-over)	10 months	30 months	36,369	3,069	28,045
Cross-over portion	40%	60%	48,007	8,082	28,045
Febrile neutropenia	12%	30%	27,501	28,045	28,045
General mortality	0.0025/month	0.007/month	25,585	40,202	28,045
Mortality after progression	0.03/month	0.06/month	27,250	29,001	28,045

Table 7: Ranges for parameters and effect on ICER for one-way sensitivity analysis. IR versus FCR.

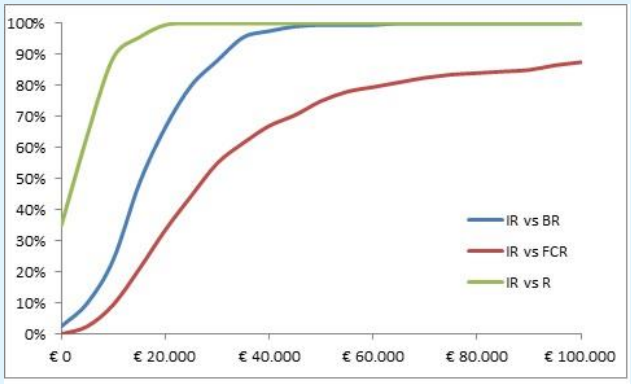

Figure 3: Acceptability curve from probabilistic sensitivity analysis.

Note: the graph plots on the Y-axis the probability of achieving and ICUR lower than the €/QALY one reported on the X-axis.

Discussion

A wide series of treatments is recommended for R/R CLL [8]. However, which treatments provide reasonable value for money in the specific clinical and economic setting is still to be ascertained. This issue is expected to become a socio-economical concern in a large number of countries, since several agents have been recently approved for the treatment of common indolent lymphoproliferative disorders. The introduction of a new health technology in oncology often increases the costs of care [21], less than 10% of the novel treatments being more effective and also less costly than standard ones. However, inpatient hospital stays are the main cost drivers of CLL, besides pharmaceuticals, therefore novel drugs might significantly reduce the former in a possibly net favorable way [22].

The present study addressed idelalisib, a first-in class oral PIP3k inhibitor to be administered in combination with Rituximab for the first treatment cycles and subsequently extended in monotherapy until CLL progression. Significant improvements in PFS and OS were reported both in heavily pre-treated [6] and in naïve patients [23], irrespectively of high-risk molecular features. Since this agent has recently become available in most European countries, we assessed whether its use in the second-line setting might be cost-effective in the Italian healthcare setting, in particular as compared with "real-life" comparator treatments and full treatment sequences, i.e. including second- and third-line therapies. We, therefore, compared IR with the

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second-line treatments that are most commonly adopted in Italy, namely BR and FCR as well as with R, which was the control arm of IR in the reported randomized trial. The model estimated that the introduction of IR in second line setting would prolong life expectancy by up to 2 years per patient at an incremental cost that is much lower than €40,000 per QALY gained. The results of our analysis are in line with other economic analyses which were held in Portugal, France, Scotland, England and Canada and that also supported the favorable cost-effectiveness of IR as compared with R, BR, FCR [24-28]. The results of the present study are also consistent in terms of cost/QALY with the reported cost for value of other anti-leukemic agents [29], since innovative treatments for blood cancers provide a reasonable value for money is achieved so long as treatments prevent future treatment lines and avoid toxicities [30]. Moreover, the higher the number of approved drugs, even belonging to the same class, the higher the survival benefit cancer patients achieve [31].

The present study, however, has several limitations. The treatment-related mortality was assumed to be the same for all the compared regimens without considering the benefit of IR as compared to R in terms of overall survival [6]. Furthermore, in the base-case analysis, it was assumed that only 50% of the patients who progressed after second-line treatment were eligible to receive a third-line therapy, while the other half moved to palliative chlorambucil; results, though, were not sensitive to even wide variations of those percentages. Another limitation was that the frequency of adverse events was not adjusted according to the treatment line, while the rates observed in heavily pre-treated patients might be overestimated. Utilities were derived from a British population, thus possibly not reflecting utility values of Italian CLL patients. However, the results in terms of life years are in line with those of QALYs. Furthermore, the model did not include all the possible therapeutic options which have been studies in relapsed/refractory CLL: in particular, another BTK-inhibitor, ibrutinib, was not included in the simulation because it was not available in Italy by the time the model was developed and could not considered a "standard of care" to be compared with novel drugs, i.e. idelalisib [32]. The present study also addressed a limited sequence of treatments, mainly second and third-line therapy; however, this was aimed at keeping the model more transparent. Finally, the results of the analysis were obtained from the perspective of the Italian health care system, without taking into account possible indirect costs related to lost productivity of CLL patients and their caregivers. We expect that the economic value of IR as compared to the other treatments would be even more favorable in the societal perspective, since idelalisib is an oral treatment.

Conclusion

This study aimed at investigating the relative cost-for-benefit of different treatment options for R/R CLL, including idelalisib, the novel oral inhibitor of phosphatidylinositol 3-kinases delta.

The findings of our research showed that treatment with IR for CLL patients who relapsed after or were refractory to first-lines therapies is a cost-effective option in the Italian healthcare setting as compared to the second-line treatments that are most commonly adopted in Italy.

Funding

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Authors' contributions

MaM conceived the model and ran the analyses. MoM, CA and MFR contributed in selecting clinical studies of progression-free survival after different treatments and contributed to writing the paper (introduction section). Marchetti M and PMP provided the unit cost data for the model and revised the final model.

Competing interests

The study was supported by a grant from GILAD Italy. Marchetti M and PMP were an employees of Gilead Italy at the time of the research.

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