COST-EFFECTIVENESS OF ORPHAN DRUGS FOR LEUKEMIA TREATMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Leukemia is a rare disease related to hematologic cancer stemming from the bone marrow. The Vietnam Ministry of Health (MOH) promulgated the Orphan Drugs List, in which there were 37 orphan drugs indicated for leukemia. This study aimed to systematically review all studies on the cost-effectiveness analysis (CEA) of these orphan drugs in leukemia treatment. **Materials and methods:** This study conducted a systematic review on all studies published till August 2021 on the National Center for Biotechnology Information (NCBI), SpringerLink, and Biomed Central. 23 studies were selected in this systematic review, which were studies that had available full-texts, were written in English, aimed to analyze the cost-effectiveness of leukemia drugs listed on the Vietnam MOH's Orphan Drugs List. The results were presented by describing CEA findings by five different leukemia types, with a focus on the incremental cost-effectiveness ratio (ICER) of each orphan drug and the comparison to the willingness-to-pay (WTP) threshold. All the cost currency values were converted to USD in 2021 to make comparison. **Results:** Of 37 drugs on the Vietnam MOH's orphan drug list, 24 drugs were cost-effectiveness analyzed with available full-texts. Of 23 selected studies in the review, there were 10 studies regarding lymphocytic leukemia (43.5%) and 13 studies regarding myeloid leukemia (56.5%). 60.9% studied on relapsed/refractory patients, 39.1% conducted cost-analyses with a social perspective, and 47.7% used overall survival combined with progression-free survival (OS-PFS) as a clinical endpoint. Quality-adjusted life year (QALY) was used as an effectiveness measurement unit in 65.2% of the total selected studies. 15 studies made a conclusion that their studied orphan drugs were cost-effective. 100% of the studies regarding acute lymphoblastic leukemia showed the orphan drugs of interest were cost-effective (ICER < WTP threshold); while about 50% of the studies regarding other leukemia types showed the orphan drugs of interest were not cost-effective (ICER > WTP threshold) and thus required suitable financial aid. **Conclusion:** This study provided information on the cost-effectiveness of 24 out of 37 orphan drugs for leukemia treatment listed on the Vietnam MOH's Orphan Drugs List. These orphan drugs could be considered as a financial burden for leukemia patients and other potential payers such as the Vietnam Social Security due to their considerably high cost.

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I. INTRODUCTION

Leukemia is a rare disease related to hematologic cancer stemming from the bone marrow. Regarding the World Health Organization (WHO), more than 474,000 leukemia cases were newly diagnosed in 2020 worldwide, in which, the number of leukemia cases and its mortality rate in Asian countries ranked first globally (49% and 54%, respectively)[1].

Several therapies have been used to control leukemia, including chemotherapy, biological therapy, radiation therapy, targeted

therapy, and stem cell transplant, in which most drugs are classified as orphan drugs with considerably high costs. In 2019, the Vietnam Ministry of Health (MOH) promulgated the Orphan Drugs List, in which there were 37 drugs used for leukemia treatment. This list provided a basis for assessing and prioritizing the issuance of circulation dossiers for these drugs, as well as increase patients' access to these orphan drugs. These 37 drugs are also classified as orphan drugs used for leukemia treatment by the Food and Drug Administration (FDA).

Numerous studies have been performed to assess the cost-effectiveness of orphan drugs in leukemia treatment. This information could support the effort of reducing the financial burden for leukemia patients as well as other potential payers. Policymakers in Vietnam could also consider this cost-effectiveness evidence to implement optimal pricing negotiations with suppliers or adjusting the health insurance coverage of leukemia patients.

This study was carried out to systematically review all cost-effectiveness analysis (CEA) studies of these 37 orphan drugs for leukemia treatment globally.

II. MATERIALS AND METHODS

This study conducted a systematic review on all CEA studies published till August 2021 on the National Center for Biotechnology Information (NCBI), SpringerLink, and Biomed Central, with the following search formula: (“cost-effectiveness’’ or “cost-utility” or “cost analysis”) AND (“drug name” or “orphan drug”) AND “leukemia treatment”. Corresponding to 37 leukemia drugs listed on the MOH's Orphan Drugs List, 37 different search formulas were formed and 2099 original studies were identified. After removing duplicates, there were 401 studies being screened then assessed for eligibility by two following main criteria: the full-text must be available and written in English, and the study must analyze the cost-effectiveness of studied orphan drugs used in leukemia treatment. As a result, 23 studies were selected in this systematic review. (Figure 1)

The results of this systematic review were presented by describing the distribution of selected studies by leukemia types, main characteristics of selected studies, CEA methods, and CEA findings. There were five major leukemia types identified, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). The main characteristics of selected studies included leukemia type, treatment condition, payment perspective, clinical endpoint, and effectiveness measurement unit. Characteristics of CEA methods were described by model type, scenario analysis, sensitivity analysis, time-horizon, and discount rate. The CEA findings, including the ICER of each orphan drug and the comparison to the corresponding WTP threshold, were reported by leukemia types, along with information on the country, year of study, and sample size.

All the cost currency values were converted to USD in 2021.

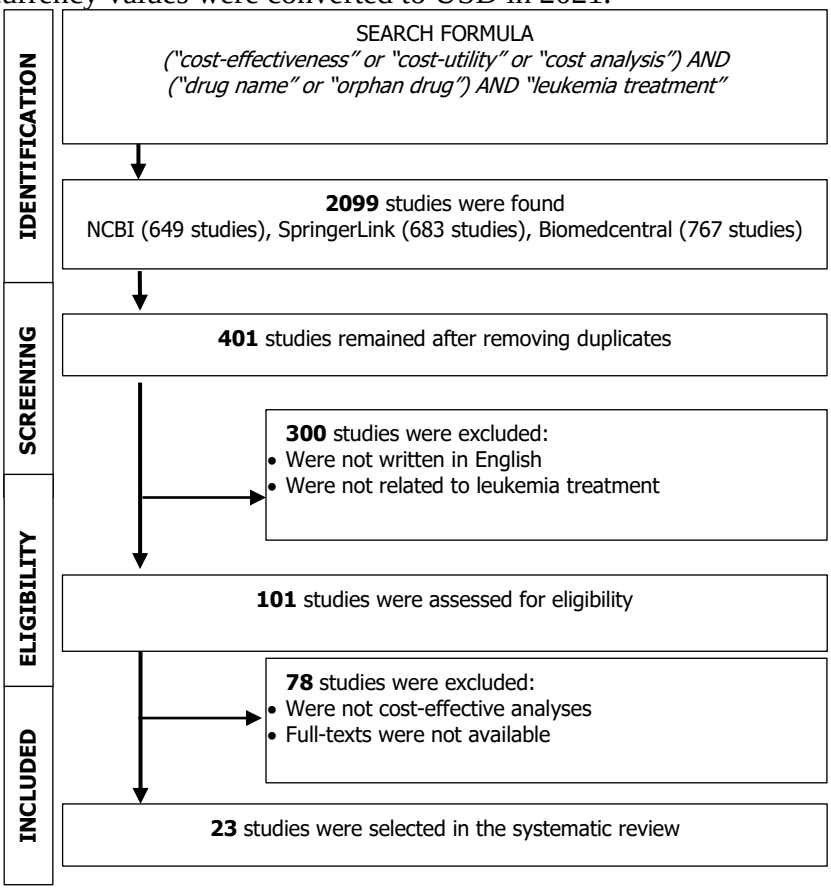

Figure 1. The systematic review study selection process following the PRISMA diagram

III. RESULTS

Orphan drugs applied in full-text CEA: Out of 37 orphan drugs, 24 orphan drugs were cost-effectiveness analyzed with available full-texts. According to the Vietnam MOH's Orphan Drug List, there were four drugs indicated for two different leukemia types, which were Imatinib (for ALL and CML), Ponatinib (for ALL and CML), Dasatinib (for ALL and CML), and Venetoclax (for AML and CLL). This review showed that the cost-effectiveness of Venetoclax was analyzed for both AML and CLL, the cost-effectiveness of Imatinib and Dasatinib were analyzed for CML, while the cost-effectiveness of Ponatinib was not yet analyzed for any leukemia type. There were several studies analyzing the cost-effectiveness of more than one orphan drug at a time[2-7, 11-13, 15 , 17, 18, 20-23]. (Table 1)

Table 1. Description of 37 orphan drugs of interest by leukemia types and the availability of CEA findings

Leukemia types	Orphan drugs listed on the MOH's Orphan Drugs List (n=37)	
	With available CEA findings (n=24)	**Without available CEA findings (n=13)**
ALL (n=12)	Blinatumomab[2, 4, 6] ,Erwinia L-asparaginase[3, 5], PEGasparaginase[3, 5], Inotuzumab ozogamicin[4], Clofarabine[6]	Nelarabine, Vincristine, Methotrexate, Mercaptopurine, *Ponatinib, *Imatinib, *Dasatinib

Leukemia types	Orphan drugs listed on the MOH's Orphan Drugs List (n=37)	
	With available CEA findings (n=24)	Without available CEA findings (n=13)
AML (n=9)	Cytarabine[12-15], Daunorubicin[12, 13, 15], Midostaurin[13], Glasdegib[14], Gemtuzumab ozogamicin[15], Venetoclax[16]	Gilteritinib, Enasidenib, Ivosidenib
APL (n=2)	Arsenic trioxide[17, 18], All-trans-retinoic-acid[17, 18]	
CLL (n=11)	Idelalisib[7], Rituximab[7, 11], Ofatumumab[8], Ibrutinib[9, 10], Acalabrutinib[10], Bendamustine[11], Venetoclax[11]	Alemtuzumab, Duvelisib, Fludarabine, Obinutuzumab
CML (n=7)	Imatinib[19, 21, 23], Nilotinib[20-22], Dasatinib[20-23], Interferon alfa-2a[20], Bosutinib[24]	*Ponatinib, Omacetaxine
*Note: * drugs indicated for two different leukemia types*		

Main characteristics of selected studies: Of 23 selected studies, 60.9% studied on relapsed/refractory patients, 39.1% conducted cost-analyses with a social perspective, and 47.7% used overall survival combined with progression-free survival (OS-PFS) as a clinical endpoint. Quality-adjusted life year (QALY) was used as an effectiveness measurement unit in 65.2% of the total selected studies, while life-year gained (LYG) and QALY - LYG were used in 4.4% and 30.4%, respectively. There were 10 studies regarding lymphocytic leukemia (43.5%)[2-11] and 13 studies regarding myeloid leukemia (56.5%)[12-24]. (Table 2)

Table 2. Main characteristics of 23 selected studies

Charateristics of studies	Total		References
	n	*(%)*	
Treatment condition			
Untreated/ Newly diagnosed	9	*(39.1)*	[5, 12, 14-17, 19, 21, 24]
Relapsed/ Refractory	14	*(60.9)*	[2-4, 6-11, 13, 18, 20, 22, 23]
Payment Perspective			
Patient	8	*(34.8)*	[2, 4, 6, 9, 14, 16, 18, 24]
Provider	4	*(17.4)*	[15, 19, 20, 23]
Social organization	9	*(39.1)*	[3, 5, 8, 10-12, 17, 21, 22]
Not mentioned	2	*(8.7)*	[7, 13]
Clinical endpoints			
OS (Overall survival)	4	*(17.4)*	[12, 13, 17, 18]
EFS (Event-Free Survival)	2	*(8.7)*	[3, 15]
OS-PFS (Progression-Free Survival)	11	*(47.7)*	[7-11, 14, 19, 20, 22-24]
OS-EFS	4	*(17.4)*	[2, 4-6]
OS-PFS-EFS	1	*(4.4)*	[16]
Others	1	*(4.4)*	[21]
Effectiveness measurement unit			
Quality-Adjusted Life Year (QALY)	15	*(65.2)*	[2, 4, 5, 9, 10, 12, 14-16, 18-21, 23, 24]
Life-Year Gained (LYG)	1	*(4.4)*	[3]
QALY - LYG	7	*(30.4)*	[6-8, 11, 13, 17, 22]
Leukemia types			
Acute lymphoblastic leukemia	5	*(21,7)*	[2-6]
Acute myeloid leukemia	5	*(21,7)*	[12-16]
Acute promyelocytic leukemia	2	*(8,7)*	[17, 18]
Chronic lymphocytic leukemia	5	*(21,7)*	[7-11]
Chronic myeloid leukemia	6	*(26,2)*	[19-24]

Characteristics of CEA methods: Of 23 selected studies, 52.1% used a partitioned survival model (PSM) and 39.1% used a deterministic sensitivity analysis (DSA) in combination with a probabilistic sensitivity analysis (PSA). (Table 3).

Table 3. *Characteristics of CEA methods used in 23 selected studies*

Characteristics of CEA methods	Total		References
	n	(%)	
Model type			
Markov	10	*(43,5)*	[5, 7, 9, 12, 15, 17-19, 21, 23]
Decision-tree	1	*(4,4)*	[3]
Partitioned survival model (PSM)	12	*(52,1)*	[2, 4, 6, 8, 10, 11, 13, 14, 16, 20, 22, 24]
Scenario analysis			
Scenario analysis applied	17	*(73,9)*	[2, 3, 5, 6, 9-11, 13-17, 19, 21-24]
Scenario analysis not applied	6	*(26,1)*	[4, 7, 8, 12, 18, 20]
Sensitivity analysis			
Probabilistic Sensitivity Analysis (PSA)	3	*(13)*	[8, 14, 23]
One Way Analysis (OWA)	4	*(17,4)*	[3, 9, 12, 19]
Deterministic Sensitivity Analysis (DSA)	1	*(4,4)*	[22]
OW - PSA	4	*(17,4)*	[15, 16, 20, 24]
PSA - DSA	9	*(39,1)*	[2, 4-7, 10, 11, 13, 17]
Others/ Not mentioned	2	*(8,7)*	[18, 21]
Time-horizon			
<10 years	10	*(43,5)*	[3, 5, 6, 12-14, 18, 19, 22, 23]
10-15 years	1	*(4,4)*	[8]
>15 years	12	*(52,1)*	[2, 4, 7, 9-11, 15-17, 20, 21, 24]
Annual discount rate			
1-1,9 %	2	*(8,7)*	[14, 19]
2-2,9 %	1	*(4,4)*	[6]
3-4 %	18	*(78,2)*	[2-5, 7-11, 13, 15-17, 20-24]
Not mentioned	2	*(8,7)*	[12, 18]

Summary of CEA findings: Of 23 selected studies, 15 studies made a conclusion that their studied orphan drugs were cost-effective. 100% of the studies regarding acute lymphoblastic leukemia showed the orphan drugs of interest were cost-effective (ICER < WTP threshold); while about 50% of the studies regarding other leukemia types showed the orphan drugs of interest were not cost-effective (ICER > WTP threshold). Blinatumomab, Ibrutinib, Imatinib, and Venetoclax were the most common drugs of interest (9 studies, 39.1%) and had a total cost less than the corresponding WTP threshold. (Table 4)

Table 4. *Summary of CEA findings from 23 selected studies*

Country, Year of study (Sample size)	Orphan drug of interest	Comparator	ICER (USD/QALY) USD/LYG)	WTP threshold (USD)
Acute Lymphoblastic Leukemia (ALL)				
USA 2017 (n=405)[2]	Blinatumomab*	Standard of Care	110,108 (USD/QALY)	150,000
The Netherlands 2019 (n=68)[3]	Erwinia asparaginase*	PEG asparaginase	1,892 (USD/LYG)	-
USA 2019 (n=731)[4]	Blinatumomab*	Inotuzumab ozogamicin	4,006 - 20,737 (USD/QALY)	150,000
UK 2019 (n= 2,911)[5]	PEG asparaginase*	Native asparaginase	-130,753 (USD/QALY)	27,800
Japan 2020 (n= 228)[6]	Tisagenlecleucel*	Blinatumomab	18,723 (USD/QALY) 19152 (USD/LYG)	67,500
		Clofarabine	24,331 (USD/QALY) 24,315 (USD/LYG)	
Acute Myeloid Leukemia (AML)				
USA 2014 (n=1,000)[12]	Decitabine	Daunorubicin + Cytarabine	-433,756 (USD/QALY)	-
Spain 2019 (n= 717)[13]	Midostaurin + Cytarabine + Daunorubicin*	Cytarabine + Daunorubicin	46,782 (USD/QALY) 39,424(USD/LYG)	60,000
Canada 2020 (n= 255)[14]	Glasdegib + Cytarabine*	Cytarabine	65,048 (USD/QALY)	80,000
		Azacitidine	65,129 (USD/QALY)	
Spain 2021 (n= 280)[15]	Gemtuzumab ozogamicin + Cytarabine + Daunorubicin*	Cytarabine + Daunorubicin	29,043 (USD/QALY)	12,000-36,000
USA 2021 (n= 400)[16]	Venetoclax + Azacitidine†	Azacitidine	260,343 (USD/QALY)	150,000
Acute Promyelocytic Leukemia (APL)				
USA 2015 (n=672)[17]	All-trans-retinoic-acid + Idarubicin	All-trans-retinoic-acid + Cytarabine	3,122 (USD/QALY) 2,933 (USD/LYG)	50,000-150,000
	Arsenic trioxide + All-trans-retinoic-acid*	All-trans-retinoic-acid + Idarubicin	5,614 (USD/QALY) 4,512 (USD/LYG)	
Mexico 2020 (n= 20)[18]	Arsenic trioxide + All-trans-retinoic-acid	International Consortium on Acute Promyelocytic Leukemia*	Italy: 6,497 USA: 19,133 Canada: 17,123 (USD/QALY)	7,060
Chronic Lymphocytic Leukemia (CLL)				
Spain 2018	Idelalisib + Rituximab*	Rituximab	36,000	54,000

Country, Year of study (Sample size)	Orphan drug of interest	Comparator	ICER (USD/QALY) USD/LYG)	WTP threshold (USD)
(Not mentioned)[7]			(USD/QALY) 17,694 (USD/LYG)	
UK 2017 (n= 233)[8]	Ofatumumab	Best Supportive Care	181,483 (USD/QALY) 88,323 (USD/LYG)	-
USA 2018 (n= 269)[9]	Ibrutinib†	Clorambucil	189,000 (USD/QALY)	150,000
UK 2019 (n= 61)[10]	Acalabrutinib†	Ibrutinib	85,912 (USD/QALY)	69,350
USA 2019 (n= 389)[11]	Venetoclax + Rituximab*	Bendamustine + Rituximab	62,043 (USD/QALY) 46,016 (USD/LYG)	150,000
		Ibrutinib	Dominant	
		Ibrutinib + Rituximab	Dominant	
		Idelalisib + rituximab	Dominant	
Chronic Myeloid Leukemia (CML)				
UK 2003 (n=497)[19]	Imatinib†	Daunorubicin + Cytarabine + Tioguanine	40,788 - 58,712 (USD/QALY)	-
UK 2011 (Not mentioned)[20]	Nilotinib	Interferon-α*	145,533 (USD/QALY)	41,700
	Dasatinib		114,814 (USD/QALY)	
USA 2015 (Not mentioned)[21]	Imatinib→ Chemotherapy/Stem Cell Transplant	Non-Tyrosine Kinase Inhibitors	171,700 (USD/QALY)	122,755
	Imatinib→Nilotinib→Chemotherapy/Stem Cell Transplant†	Imatinib→ Chemotherapy/Stem Cell Transplant	253,500 (USD/QALY)	
	Nilotinib→Dasatinib→ Chemotherapy/Stem Cell Transplant†	Imatinib→Nilotinib→ Chemotherapy/Stem Cell Transplant	445,100 (USD/QALY)	
USA 2017 (n=597)[22]	Nilotinib*	Dasatinib	-7,031 (USD/QALY) -5,753 (USD/LYG)	-
China 2017 (n= 670)[23]	Dasatinib†	Imatinib	58,989 (USD/QALY)	22,455
USA 2021 (n=1,802)[24]	Bosutinib*	Dasatinib	19,811 (USD/QALY)	50,000-150,000
		Nilotinib	41,932 (USD/QALY)	

Notes ** The optimal therapy* *† Requiring financial aids*

IV. DISCUSSION

This study provided a systematic review of CEA studies of leukemia drugs listed on the Vietnam MOH's Orphan Drug List. 23 studies were reviewed, with the sample size varied from approximately 20 to 3000 leukemia patients with different distributions of gender and age. These studies were clinical trials that followed evidence-based principles and practice of publishing all information about the phase, sample size, and corresponding results on the United States National Library of Medicine. Most of the selected studies were conducted in developed countries such as the United States, the United Kingdom, and Spain (with 10, 5, 3 studies, respectively).

The conclusion of the cost-effectiveness of a drug depended on the WTP threshold used in each study. The WTP threshold of studies in the United States was the highest (150,000 USD) compared to the rest of countries in this review and was 20 times higher than that of Mexico (7,060 USD). Therefore, an orphan drug that was considered as cost-effective in the United States might not be considered as cost-effective in other countries. In addition, the use of different effectiveness measurement units was another factor leading to different conclusions on the cost-effectiveness of studied orphan drugs. This systematic review recorded that ICER per QALY value was higher than ICER per LYG value[6-8, 13, 17, 22] and in two studies, the ICER per QALY value was double the ICER per LYG value[7, 8].

This review showed that conducting up-to-date CEA studies of orphan drugs in leukemia treatment was necessary for the effort of reducing the financial burden. Tisagenlecleucel was approved in Japan in 2019 for the ALL treatment and its CEA study was carried out in the same year, comparing this new intervention to the two first-line ALL treatment drugs, Blinatumomab and Clofarabine, by Wakase S, *et al.*[6]. The results showed that Tisagenlecleucel was highly cost-effective, with the ICER compared to Blinatumomab and Clofarabine were estimated at $18,723/QALY and $24,331/QALY respectively, which were all significantly lower than the Japanese WTP threshold of 68,297 USD. In another case, the conclusion on the cost-effectiveness of Ibrutinib therapy in the United States varied by year, which kept the healthcare system stay updated on the cost-effectiveness aspect of leukemia drug therapies. In 2018, Barnes JI, *et al.* calculated an ICER of 189,000 USD/QALY between Ibrutinib and Chlorambucil, which was greater than the corresponding WTP value, thus, suggested that payers should be offered financial aid in order to approach the better treatment[9]. In 2019, Huntington S.F., *et al.* showed evidence that Venetoclax + Rituximab was cost-effective compared to Ibrutinib, in the context of Venetoclax was approved for leukemia treatment by the FDA that year[11].

To date, Vietnam does not have its own WTP threshold, therefore, it is recommended by the WHO to use a threshold of less than three times the national annual gross domestic product (GDP) per capita. This systematic review showed that most of the studied orphan drugs would not be considered as cost-effective in Vietnam if pure comparing the ICER values to the threshold of three times the Vietnam GDP per capita of 3,500 USD in 2021. However, taking into account that these studies were

conducted in different populations and periods of time, information from this review should be only served as a reference to firstly understand the cost aspect of these orphan drugs worldwide, and then to conduct future research in Vietnamese populations. Only when aiding by high-quality and up-to-date CEA results then policymakers could make proper decisions on pricing negotiation or health insurance coverage in order to provide better care to leukemia patients.

V. CONCLUSION

The study provided an up-to-date review of the cost-effectiveness of 24 out of 37 orphan drugs for leukemia treatment listed on the Vietnam MOH's Orphan Drugs List. With considerably high costs, these orphan drugs could be a financial burden for leukemia patients and other potential payers such as the Vietnam Social Security. Therefore, financial aid policies are necessary to help patients timely access treatment, and better pricing negotiations with suppliers are needed to implement to reduce the financial burden of these orphan drugs.

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