BÀI BÁO NGHIÊN CỨU GỐC

Cost-effectiveness of brentuximab vedotin in treating increased risk of relapse/progression of classical hodgkin lymphoma patients post autologous stem cell transplant

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ABSTRACT

Objective: Hodgkin lymphoma patients who relapsed/progressed early after autologous stem cell transplant (ASCT) usually have poor prognoses. Results from clinical trials have demonstrated Brentuximab vedotin (BV)'s significant clinical effectiveness for consolidation therapy after ASCT for patients who have high risk of relapse/progress. An economic evaluation study for Vietnamese CHL patients is necessary and can provide useful evidence for policymakers. **Methods:** A multi-stage economic evaluation model consisting of two partitioned survival models was used to estimate incurring costs and effectiveness from health insurance perspective for two hypothetical groups of Vietnamese adult CHL patients who have high risk of relapse/progression, one received standard care and the other received BV consolidation plus standard care as post-ASCT care. Necessary healthcare services were identified via Ministry of Health guidelines and Vietnamese clinical opinions. Efficacy parameters were taken from published systematic review and randomized controlled trials results. Model costs and utility inputs were adapted for Vietnamese context via relevant published literature, guidelines, regulations, and clinical opinions. Model cycle of 1 week and life-time horizon was used. Discounting rate of 3% was applied for cost and effectiveness.

Results: Consolidation with BV post-ASCT was estimated to increase treatment cost by 654,502,745 VND per patient, increased 1.295 life years and 2.153 QALYs. Incremental cost-effectiveness ratios were estimated at 505,465,854 VND/LY and 304,045,395 VND/QALY. **Conclusions:** BV consolidation was not cost-effective compared to 3GDP threshold, however, with an appropriate risk-sharing mechanism, the intervention can be cost-effective, improve patients access to the effective treatment and maintain equity in healthcare.

Keywords: *Classic Hodgkin lymphoma; increased risk relapse/refractory, brentuximab vedotin, cost-effectiveness.*

INTRODUCTION

Hodgkin lymphoma (HL) is a hematologic neoplastic disease and HL cases are estimated to account for about 10% of all lymphoma cases in the United States (1). Classical Hodgkin lymphoma (CHL) is one of the most common type of HL, accounting for over 90% of HL cases (1,2). About 90% of CHL patients can be treated with first-line chemotherapy and radiotherapy (2). According to GLOBOCAN (The Global Cancer Observatory) in 2020, there were 651 new cases and 251 deaths by Hodgkin's lymphoma (HL) each year in Vietnam (3).

Even though CHL is highly curable, there are still patients whose treatment failed. The

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Submited: 21 March, 2022
Revised version received: 23 July, 2022
Published: 30 August, 2022
DOI: https://doi.org/10.38148/JHDS.0604SKPT22-027

second line treatments for these patients usually involved high dose chemotherapy regimens and autologous stem cell transplant (ACST) (1). Patients who respond well to these therapies are achieving the best treatment outcomes and about 50% of the patients can be treated (1). However, for those who are not responding to the second line therapies or relapsed/progressed after ASCT, the prognosis is poor, especially among those relapse within the first 6 months after ASCT (4).

Currently, Adcetris® (brentuximab vedotin, BV) has been approved for consolidation treatment in patients who received ASCT and have high risk of relapse/progression by the Food and Drug Administration (FDA) and the European Commission (5,6). Furthermore, BV has been approved other CHL indications: Used in combination with chemotherapy for previously untreated stage III or IV CHL patients CHL patients after ASCT failure or at least two prior chemotherapy regimens failure and unable to receive ASCT (5).

Brentuximab vedotin has been approved for use in Vietnam, according to Decision 692/QĐ-QLD. However, at the moment, BV has not yet a treatment option for CHL patients and not being reimbursed by Social Health Insurance. According to Ministry of Health Guidelines on diagnosis and treatment of hematologic diseases, relapsed/refractory CHL patients will receive high-dose chemotherapies (ABVD, ESHAP, DHAP) and autologous stem cell transplant if possible. There are no specific treatment guidelines for patients having increased-risk of relapse/progression post-ASCT.

The evidence from AETHERA, a phase III randomized controlled trial, showed that high-risk relapse/progression post-ASCT patients who received consolidated BV has longer progression-free survival (7). Patients in BV consolidation treatment arm had significantly higher 5-year PFS (59%, 95% CI: 51-66) compared to placebo control arm (41%, 95% CI: 33-49). In subgroup analysis, patients with 2 or more risk factors also achieved significantly higher 5-year PFS (HR, 0.424; 95% CI: 0.302-0.596) (7).

Although post-ASCT BV consolidation treatment has significant clinical effectiveness, evidence on cost-effectiveness of the treatment is still limited worldwide and completely omitted in Vietnam. A cost-effectiveness study conducted from a U.S. healthcare payer perspective reported that upfront BV consolidation (after ASCT) led to a higher cost of $378,832 compared to $219,761 of BV as salvage therapy (after relapsed post-ASCT) (8). In a health technology assessment by National Institute of Health and Care Excellence (NICE), the use of BV consolidation in increased risk of relapse/progression patients was estimated to require an additional £35,606 per quality-adjusted life year (QALY) gained, higher than the preferred cost-effectiveness range (£20,000-£30,000/QALY gained) (9).

This economic evaluation was conducted to provide cost-effectiveness evidence of BV consolidation therapy in CHL patients and have high risk of relapse/progression in Vietnam.

METHODS

Study design

The study evaluated the incurring cost and health outcomes for hypothetical adult Vietnamese CHL patients who have received ASCT and have high-risk of relapse/progression post-ASCT. This hypothetical population have similar characteristics to Vietnamese CHL patients, such as mean age of 47.6 years old; body weight of 50.0 kg; and 54.4% of patients were male (according to responses from 06 Vietnamese clinical

Mã DOI: https://doi.org/10.38148/JHDS.0601SKPT21-083

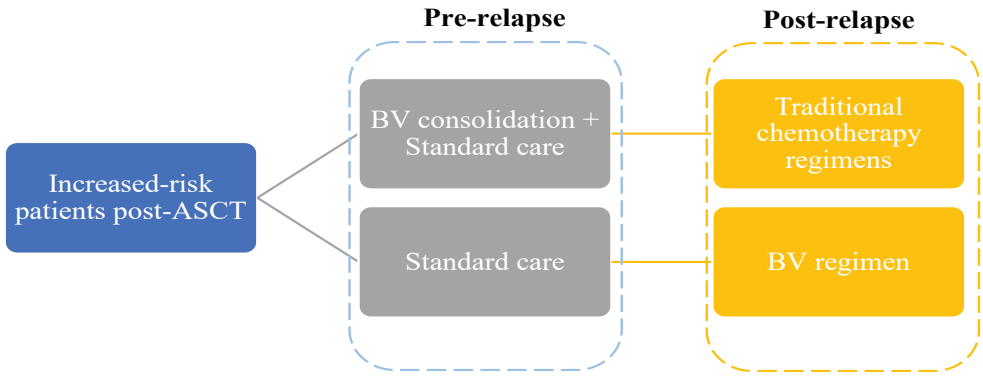
experts). Costs and health outcomes gained in both pre-relapse and post-relapse phases were estimated. The study included pre-relapse phase because BV has clinically proven effectiveness in prolonging progression-free survival and the inclusion of cost and effectiveness in post-relapse phase would better capture the cost-effectiveness of BV as there would be differences in subsequent treatment costs and health outcome gained.

A multiple stages economic evaluation model was used: the first stage stimulated the pre-relapse phase, and the second stage stimulated the post-relapse phase of the patients (Figure 1). Two partitioned survival models were used jointly to stimulate the transition, incurring costs and health outcomes for patients during each stage.

In the first stage, the patients could either receive standard of care (SC, or control group), which included the use of trimethoprim sulfamethoxazole (T-S) 960mg, once every two days, and routine follow-ups (up to 5 years); or the patients could receive BV consolidation (intravenous transfusion, once every 28 days, 1.8mg/kg, up to 16 cycles) plus standard care (BV + SC, or intervention group).

In the second stage, the patients from control group would receive BV as their salvage therapy post-relapse (intravenous transfusion, once every 28 days, 1.8mg/kg, up to 16 cycles), while the patients from the intervention group received traditional chemotherapy regimens. The details of this model has been published elsewhere.

Figure 1. Intervention and comparator arms in the model



Note: ASCT: autologous stem cell transplant, BV: brentuximab vedotin.

Economic assessment model

The model estimated costs incurred from the perspective of health insurance payer in Vietnam (Figure 3). The outcomes of the model were incremental cost-effectiveness ratios (ICER) with QALYs or additional life years (LYs) as measures of effectiveness. The starting age of the model was 47.6 years old, lifetime horizon was used, with 1-week model cycle. An annual 3% discount rate was applied for both cost and effectiveness. In base-case analysis, we used a willingness-to-pay (WTP) threshold of 3 times GDP of Vietnam (VND 193,471,110/QALY) (10).

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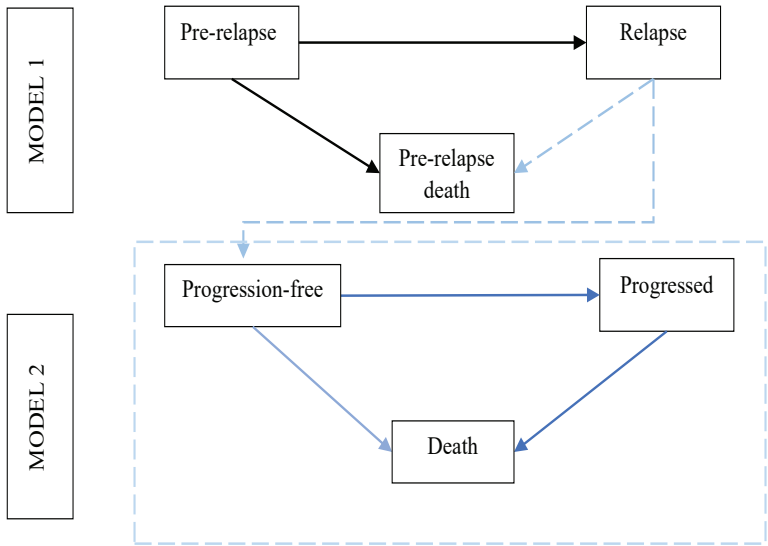
Figure 2. Model structure schematic



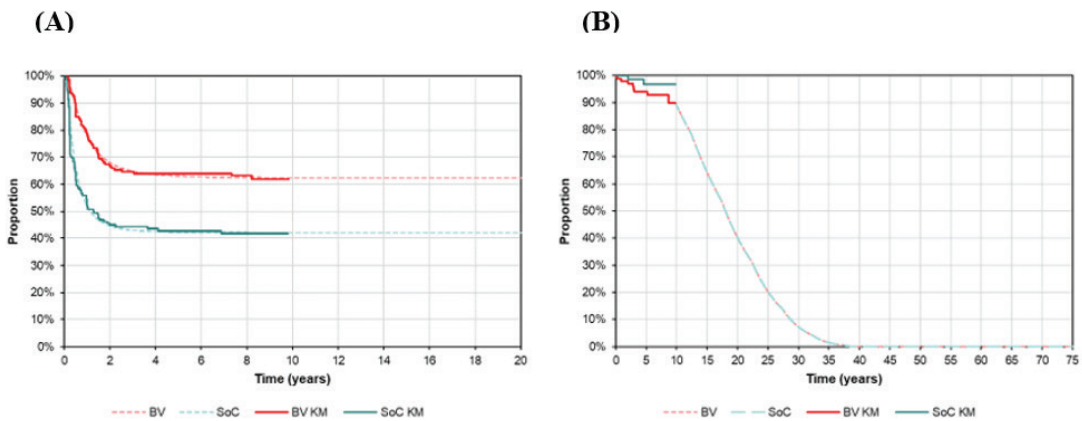
The first PSM model consisted of 3 health states: **Pre-relapse**; **Relapse** and **Pre-relapse death** (Model 1, Figure 2). All patients started in the pre-relapse phase. After each model cycle, the proportions of patients in each health state were determined by the pre-relapse survival (PrePS) and time-to-progression (TTP) Kaplan-Meier (KM) curves (more details in **Clinical parameters used**):

- "Relapse": cumulative differences of %patients in the TTP curve of two consecutive cycles.

- "Pre-relapse death": 1 - %patients in the PrePS curve at that cycle.

- "Pre-relapse": 1 - %Relapse - %Pre-relapse death.

Figure 3. TTP and PrePS Kaplan-Meier curves.



Note: (A) Time-to-progression Kaplan-Meier curve. (B) Pre-relapse survival Kaplan-Meier curve. BV: BV consolidation + standard care, SoC: Standard care, KM: Kaplan-Meier.

Mã DOI: https://doi.org/10.38148/JHDS.0601SKPT21-083

The second PSM model consisted of 3 health states: **Progression-free**; **Progressed**; and **Death** (Model 2, Figure 2). All relapsed patients in Model 1 would enter "Progression-free" health state in Model 2 and immediately receive subsequent therapies (traditional chemotherapies or BV). The proportions of patients in each health state and transition probabilities were calculated similarly in Model 1, by using overall survival (OS) and progression-free survival (PFS) KM curves (more details in **Clinical parameters used**):

- Progression-free: PFS rate at each cycle

- Progressed: cumulative differences of %patients in the PFS curve of two consecutive cycles.

Death: 1 – OS rate at each cycle.

Clinical parameters used

In Model 1, we used the estimated results for TTP and PrePS KM curves provided by Delta-Hat authors from the United Kingdom due to limited access to AETHERA trial's individual level data (7,11). The Delta-Hat group had used AETHERA trial's data on effectiveness (TTP and PrePS) of the intervention and they extrapolated TTP from Kaplan-Meier (KM) curve using a Mixture cure model (MCM) with log-normal distribution (11). For PrePS, we directly used the data from the provided PrePS KM curve, then we used mortality rate from the life table for Vietnamese (published by WHO (12)) after the end of KM curve, adjusted by 10% as the PrePS events were not sufficient to perform extrapolate beyond the trial duration(11). PrePS inputs were the same between the two study groups as we assumed that PrePS between the two groups of patients was not different. This assumption was made based on the results of the analysis from the authors (11).

For Model 2, we used KM curves of OS and PFS from SG035-003 trial and AETHERA trial for BV salvage therapy group. As for traditional chemotherapy regimens group, OS and PFS are derived from the KM curve summarized from relevant data sources proposed by Kaloyannidis et al (13).

Quality of life parameters

In pre-relapse phase, quality of life (QoL) data is used directly from the results of AETHERA trial, analyzed by the Delta-Hat authors(11). We applied the average utility value for the intervention and control group (0.89 and 0.92 (4), respectively). These utility values were adjusted to gender and age-specific utility values of Vietnamese people (15), using the age-sex utility decrements. The utility values were also adjusted to reflect the fact that these are cancer patients, hence, the patient's utility was expected to be lower than the utility of the general population in Vietnam (16), with the same gender and age, throughout the model. If the utility value being used is higher than the utility of the general population, then the utility value used will be the utility value of the general population decreased by 10%.

In post-relapse phase, QoL was calculated based on the treatment response rates summarized from literature review (13) and then applied the treatment response - utility value set of Taiwanese CHL population (17).

A one-off adverse event (AE) disutility was applied in the first cycle to simplify the model calculations and due to the lack of the AEs onset data. The disutility values were calculated based on the incidence rate, the length, and the reduction in the utility of each specific AE reported in clinical trials (2,5).

Cost parameters

This study only estimated direct medical costs, including drug/chemotherapy costs, administration costs, monitoring costs, standard care costs (i.e. T-S drugs costs and

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routine follow-up costs), hospitalization costs, AEs managing costs. Micro-costing method based on necessary health care services and drugs was used to perform cost estimations. The unit costs of drugs and chemotherapy substances that are covered by Health Insurance (in Circular No. 30/2018/TT-BYT) were collected and taken average based on their bidding prices in health facilities (published publicly on Vietnam Centralized Drugs Bid portal, Ministry of Health). For the price of medical services covered in health insurance, we used the price specified in Circular No. 13/2019/TT-BYT.

The listed price for 01 BV vial was 63,214,433 VND and assuming that Health Insurance would reimburse the amount equivalent to 50% of listed price (base-case) and the patients would receive 100% reimbursement rate (based on experts opinion), the estimated average cost for 01 BV consolidation cycle was VND 65,141,001, including the cost of chemotherapy drugs, comedications, monitoring and drug administration costs.

Table 1b. Brentuximab vedotin cost per cycle estimation

	Drug	Dosage/ Frequency	Unit cost (VND)	Proportion of patients require the service	Total (VND)
Chemotherapy drugs	Brentuximab vedotin	1.8 mg/kg	31,607,217	100%	63,214,433
Comedications	Dexamethasone	8 mg	154	100%	2,462
	Pegfilgrastim	6 mg	1,013,193	30%	1,823,747
Administration	Day-time bed cost	1 day	70,305	100%	70,305
	NaCl 0.9%	250 ml	35	100%	8,653
	Outpatient intravenous infusion	1 time	21,400	100%	21,400
Total					**VND 65,141,001**

**Note: The costs were calculated based on the assumption that HI reimbursement amount is equivalent to 50% of the current BV listed price and patients receive 100% reimbursement rate from HI.*

The AEs managing costs were estimated based on the necessary drugs and medical services via 06 clinical expert interviews. We assumed that AEs grade 1-2 will not incur costs to Health Insurance. In addition, the costs associated with end-of-life care and premature mortality was excluded.

The cost of monitoring in each treatment cycle or follow-up appointment was estimated at VND 961,200 per visit.

Mã DOI: https://doi.org/10.38148/JHDS.0601SKPT21-083

Table 2b. Monitoring cost per visit/per cycle

Drugs/Services	Dosage/ Frequency	Unit cost (VND)	Proportion of patients require the service	Total (VND)
Medical examination	1	38,700	100%	38,700
Blood tests	1	106,000	100%	106,000
Liver function tests	1	86,000	100%	86,000
Kidney function tests	1	61,200	100%	61,200
Other biochemistry tests	1	102,300	100%	102,300
CT scan	0.33*	1,701,000	100%	567,000
Total				**VND 961,200**

**CT scan is needed every 3 cycles based on clinical opinion; The costs were calculated based on the assumption that patients receive 100% reimbursement rate from HI.*

For relapsed patients, we used the results of our previously published study, which estimated the total post-relapse treatment cost of 01 patient receiving standard chemotherapy was VND 80,788,343 and for 01 patient using BV as salvage therapy was VND 319,983,721 (18). Due to lack of data, we assume that post-relapse costs and outcomes were only depend on which post-relapse treatment the patients received and independent of previous (pre-relapse) treatments and time of relapse.

Sensitivity analysis

We conducted deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) by changing the value of each parameter or all the input parameters following beta or normal distribution. For parameters that we did not have information about its distribution, we assumed that these parameters follow a normal distribution with standard error equaled to 10% of the parameter value. PSA was performed to assess the joint uncertainty of all input parameters of the model with 1,000 loops.

Scenario sensitivity analysis was also conducted by changing the post-relapse subsequent treatments and changing the hypothetical cost per vial of BV covered by health insurance (equivalent to 10% - 90% of the listed price).

RESULTS

In base-case analysis, the cost of BV was assumed to be covered by health insurance at a price equivalent to 50% of the listed price. The total cost for 01 BV consolidated patient was VND 859,637,105, increasing VND 654,502,745 versus 01 patient in control group (Table 1). The intervention was estimated to increase 1.295 additional life years, or 2.153 quality-adjusted life years. ICERs were VND 505,465,854 per LY gained or VND 304,045,395 per QALY gained. The results showed that ICER in base-case analysis did not meet the 3GDP WTP threshold (VND 193,471,110/QALY gained).

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Table 1. Base-case results of brentuximab vedotin consolidation post-ASCT.

Result	BV consolidation	Standard care	Difference
LYs	10.242	8.947	1.295
QALYs	8.426	6.273	2.153
Total cost (VND)	859,637,105	205,134,360	654,502,745
ICER - LY (VND)	-	-	505,465,854
ICER - QALY (VND)	-	-	304,045,395

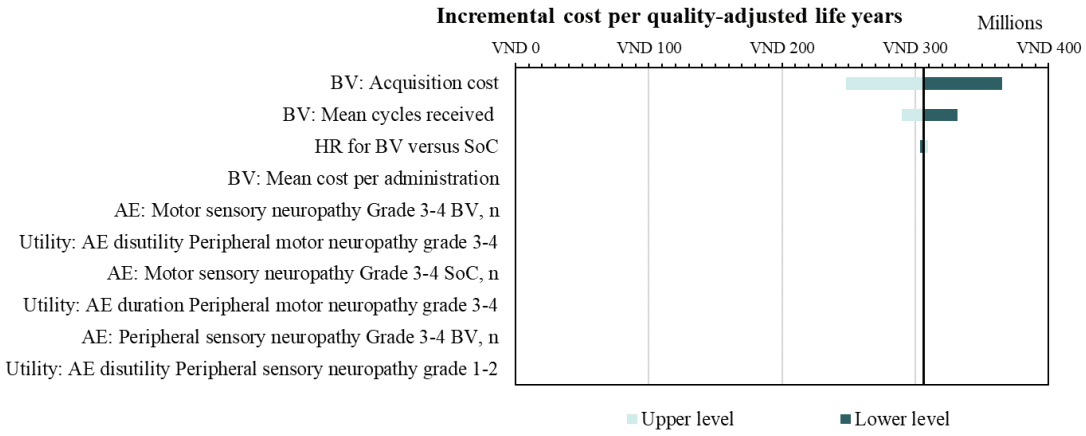
Note: Assumed that BV cost per vial covered by HI is equivalent to 50% of current listed price.

Sensitivity analysis results

One-way sensitivity analysis

The result of one-way sensitivity analysis for Model 1 showed that the final ICER-QALYs outcome of the model was most sensitive to input parameters such as the acquisition cost of 01 BV vial and the mean number of BV cycles used.

Figure 4. One-way sensitivity analysis results



Note: BV: brentuximab vedotin, HR: hazard ratio, AE: adverse event.

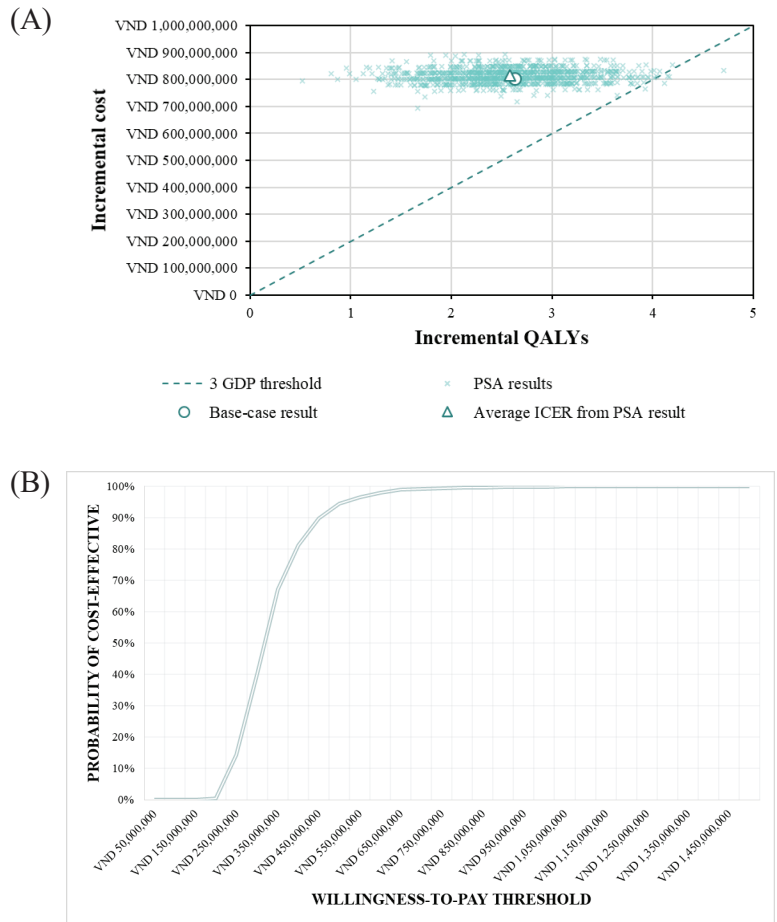
One-way sensitivity analysis for Model 2 showed that the results generated by the model was sensitive to the utility values set used for treatment responses and the acquisition cost of 01 BV vial (18).

Probability sensitivity analysis

The average ICER calculated in the PSA did not vary much from the base-case analysis result: 312,885,147 VND/QALY compared to 304,405,395 VND/QALY (Figure 5A).

PSA analysis results also showed that BV consolidation therapy has low probability of being cost-effective (2%) when using the WTP threshold of 3GDP/QALY. If we use the WTP threshold from the results of a study on non-small cell lung cancer patients in Vietnam (259,923,000 VND/QALY), this intervention would have a higher probability of being cost-effective, about 19% (Figure 5B).

Figure 5. Probabilistic sensitivity analysis and Cost-effectiveness curve.



Note: (A) Probabilistic sensitivity analysis results; (B) Cost-effectiveness curve.

Scenario sensitivity analysis

We assumed that all patients would receive standard chemotherapy regimens after relapse, regardless of their post-ASCT treatments. The analysis showed that BV consolidated patients would gain 2.041 additional life years, equivalent to 2.338 QALYs compared to patients in control group. The corresponding ICERs were VND 337,317,632/QALY gained, and VND 386,354,265/LY gained.

In other scenarios where we changed the level of health insurance coverage for BV, the intervention would be cost-effective if the price that health insurance covered for BV was equivalent to 40% or less of the current listed price; ICER-QALYs: from 234.340.307 VND/QALY at 40% to 25.225.042 VND/QALY at 10%.

Table 4b. Scenario sensitivity analysis results

Scenario	Incremental costs (VND)	Incremental QALYs	Incremental LYs	ICER-QALYs
Base case	654,502,745	2.153	1.295	304,045,395
Time horizon of 20 years	654,003,597	1.953	1.058	334,908,369

Scenario	Incremental costs (VND)	Incremental QALYs	Incremental LYs	ICER-QALYs
Time horizon of 30 years	654,464,960	2.137	1.277	306,218,140
Time horizon of 40 years	654,502,706	2.153	1.295	304,048,164
Time horizon of 50 years	654,502,745	2.153	1.295	304,045,395
Time horizon of 60 years	654,502,745	2.153	1.295	304,045,395
Discounting: All 0%	662,967,150	3.081	2.247	215,209,111
Discounting: All 3%	654,502,745	2.153	1.295	304,045,395
Discounting: All 5%	649,426,400	1.729	0.864	375,605,473
HI reimbursement amount equivalent to 90% of listed price	1,254,704,852	2.153	1.295	582,865,749
HI reimbursement amount equivalent to 80% of listed price	1,104,654,325	2.153	1.295	513,160,661
HI reimbursement amount equivalent to 70% of listed price	954,603,799	2.153	1.295	443,455,572
HI reimbursement amount equivalent to 60% of listed price	804,553,272	2.153	1.295	373,750,484
HI reimbursement amount equivalent to 50% of listed price	654,502,745	2.153	1.295	304,045,395
HI reimbursement amount equivalent to 40% of listed price	504,452,218	2.153	1.295	234,340,307
HI reimbursement amount equivalent to 30% of listed price	354,401,692	2.153	1.295	164,635,218
HI reimbursement amount equivalent to 20% of listed price	204,351,165	2.153	1.295	94,930,130
HI reimbursement amount equivalent to 10% of listed price	54,300,638	2.153	1.295	25,225,042
Cost input for drugs: MIN	647,816,377	2.153	1.295	300,939,283
Cost input for drugs: MAX	680,320,950	2.153	1.295	316,039,091
Cost input for drugs: 95% CI Lower	649,209,078	2.153	1.295	301,586,254
Cost input for drugs: 95% CI Upper	659,796,412	2.153	1.295	306,504,537

DISCUSSION

In this study, we performed an economic evaluation of BV consolidation for CHL patients who had received ASCT procedure and were considered to have high risk of relapse or progression post-ASCT. Consolidation with BV has been proven to prolong PFS in increased-risk of relapse/progression CHL patients post-ASCT compared to placebo (7), which could potentially have a positive effect on patients' OS, as early relapse is one of the major factors predicting treatment outcomes post-ASCT relapse/refractory (4). Despite

having clinical effectiveness and potential life-saving treatment outcomes, our base-case results showed that BV consolidation was not cost-effective compared to standard care.

The base-case analysis results showed that the use of BV consolidation increases LYs and QALYs for intervention patients, but the treatment was not cost–effective compared to WTP thresholds used in the study: the WTP threshold equals to 3GDP/QALY (VND 193,471,110/QALY) or WTP threshold from a previous study conducted on non-small cell lung cancer patients in Vietnam (VND 259,923,000/QALY). Economic evaluation studies previously conducted in other countries also concluded that BV consolidation may not be cost-effective. For example, in the UK, this indication had an estimated ICER of £35,606/QALY (9), equivalent to more than VND 1 billion/QALY. In the U.S., one study estimated that the use of BV consolidation had an ICER of USD 148,664/QALY (about VND 3.4 billion/QALY) (8).

Due to the lack of existing cost-effectiveness threshold in Vietnam, this study used a WTP threshold based on the country's per capita GDP, which was recommended in Choosing Interventions that are Cost-Effective project by World Health Organization (WHO-CHOICE) (19). However, relying on these thresholds is argued to be problematic and lowers the values of cost-effectiveness evaluations (19). Instead, in an alternative approach called "League tables", a comprehensive set of health interventions will be sorted based on their ICERs when comparing to "null" or "doing nothing". By implementing the interventions from the top of the table (i.e. the intervention has the lowest ICER) and go down this list of interventions until the budget is depleted, health outcomes achieved will be maximized with the specific budget constraint (19). However, this approach has its own disadvantages, as ICERs may not always be available for different settings and contexts (19), hence, the construction of a league table is sometimes challenging. In a nutshell, in order to draw a conclusion about the cost-effectiveness of an intervention, evidence on many aspects of the intervention should be provided and considered, such as the overall budget impact, disease burden, intervention costs and effectiveness, etc. Furthermore, another alternative approach called "Intervention benchmark" was also introduced, in which, a threshold being used in an economic evaluation would be a WTP threshold that has been studied and published in that settings (19). In this case, if we use the WTP threshold that has been established previously for non-small cell cancer patients (VND 259,923,000/QALY), the results from the study have been approached really close to this threshold, suggesting the potential cost-effectiveness of the intervention.

Our cost-effectiveness study has some limitations. Firstly, the study was conducted from the perspective of the health insurance payment agency in Vietnam, hence, the results of the analysis may not fully represent the potential costs from the patient perspective (e.g., out-of-pocket costs, indirect costs, loss of income/productivity etc.) as well as the benefits of intervention from societal perspective (the intervention can bring even more benefits because the majority of patients are young and are in working age). In a study previously conducted in Vietnam, 56.9% of cancer patients had catastrophic healthcare expenditure which larger than 50% of household income, and 37.4% of the studied households were impoverished by the economic burden of cancer treatments (20). Secondly, the model used multiple input parameters from international clinical trials which may not fit for Vietnamese patients. We performed DSA and PSA to overcome this limitation and the impact of these parameters

on the final outcome was mainly negligible, except the cost of BV vial (hypothetically covered by Heath Insurance), average number of BV cycles used, and patient utility corresponding to treatment response.

Based on this study findings, although BV consolidation for patients at high risk of relapse/progression after ASCT is not considered cost-effective, the results of the analysis showed that the intervention approached very close to cost-effectiveness thresholds. Furthermore, a reimbursement decision for a healthcare intervention should not be made based on solely ICER result. With a suitable risk sharing mechanism among stakeholders in place, we believe that BV consolidation therapy can be cost-effectiveness in Vietnam, thus improve and maintain the equality in patients' accessibility to this clinically effective and life-saving treatment.

CONCLUSION

The addition of BV consolidation treatment in CHL patients at high risk of relapse/progression post-ASCT in Vietnam was not cost-effective from the health insurance perspective, even though, the results had approached very close to the WTP threshold reported from non-small cell lung cancer in Vietnam. When the cost per vial of BV covered by health insurance is equivalent to 40% (or lower) of the current listed price, ICER was lower than the WTP threshold of 3GDP/QALY, suggesting that BV consolidation at this price can be cost-effective. The study has certain limitations, which has been discussed and explored with sensitivity analyses.

Conflicts of interest

This study was funded by Takeda Pharmaceuticals (Asia Pacific) Pte Co., Ltd. The research team declares that there is no conflict of interest when conducting the study and that all technical issues and research content were independent from the sponsor.

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