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ORIGINAL RESEARCH

Cost-effectiveness of letermovir as cytomegalovirus prophylaxis in adult recipients of allogeneic hematopoietic stem cell transplantation in Hong Kong

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ABSTRACT

Background: The cost-effectiveness of letermovir as cytomegalovirus (CMV) prophylaxis in adult seropositive patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), compared with the conventional strategy of preemptive treatment, has not been evaluated in Asia.

Methods: A decision analytical model, simulating the clinical progression of CMV infection on a lifetime horizon, was developed to compare prophylactic strategy with letermovir with preemptive therapy alone as anti-CMV strategies. Prophylaxis comprised administering letermovir for 14 weeks, with clinical outcomes measured at 24 weeks, followed by preemptive therapy if CMV infection occurred. This approach was modeled on outcomes of the letermovir phase 3 clinical study. The model enumerated the cost of letermovir prophylaxis, quality-adjusted life years (QALYs), and incremental cost per QALYs gained with prophylaxis. The opposite arm involved regular monitoring and preemptive therapy for CMV reactivation. Real-world costs from the adult HSCT center at Queen Mary Hospital, Hong Kong, were adopted for analysis. Costs and clinical benefits, expressed as QALYs, were discounted at 3% per year.

Results: Letermovir prophylaxis compared with preemptive therapy only would lead to an increase of life-year and QALYs at increased costs. Incremental cost-effectiveness analysis showed that letermovir prophylaxis had an associated cost of HKD 193,580 for each life-year gained, and HKD 234,675 for each QALY gained. Probabilistic sensitivity analysis showed that the majority of incremental cost-effectiveness ratio fell below the cost-effectiveness threshold of HKD 382,046 (one gross domestic product per capita) per QALY gained.

Conclusions: Letermovir prophylaxis would be cost-effective for preventing CMV infection in adult seropositive allogeneic HSCT recipients in Hong Kong.

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Introduction

Cytomegalovirus (CMV) infection is an important cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT)[1]. The manifestations range from virologic reactivation (detectable circulating CMV pp65 antigen or CMV DNA) to actual clinical disease (organ involvement with histopathologic changes)[2]. The risk of CMV infection is nearly double in allogeneic as compared with autologous HSCT[2]. Without anti-viral prophylaxis, CMV virologic reactivation in high-risk seropositive allogeneic HSCT recipient might approach 100%[2]. High-risk factors also include HLA (A, B, DR, C, or DRB1) mismatched related or unrelated donor, haploidentical donor, umbilical cord blood donation, *ex vivo* T-cell depletion, and graft-versus-host disease (GVHD) of > grade 2[3,4]. Treatment of CMV reactivation with antiviral agents may be associated with significant toxicity. For example, around 30% of patients treated with ganciclovir or valganciclovir develop treatment-associated neutropenia[5], which in turn leads to greater incidence of bacterial or fungal infections, with resultant increased mortality[6]. Use of foscarnet is also associated with nephrotoxicity in up to 27% of patients[7]. Therefore, new anti-CMV drugs with an improved toxicity profile are needed to provide effective and well-tolerated prophylaxis, particularly in high-risk seropositive allogeneic HSCT recipients.

The seropositive rates of CMV in Hong Kong has slightly fallen in the last two decades, from almost 100% in the 1990s[8] to about 89% in the 2010s[9]. In a retrospective observational study conducted in Hong Kong adults, seropositivity of CMV fell from 91.03% in 2004 to 83.15% in 2012-2017, but this decreasing trend was not observed in adults over 45 years of age whereby seropositivity rates were maintained over 95% throughout the study period[10]. These rates are comparatively higher than those in Western countries, with seroprevalence rates typically below 80%[11,12]. The high

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seropositive rate translates into a large disease burden of CMV infection in allogeneic HSCT in Hong Kong, particularly when alternative (match-unrelated and haploidentical) donors are used, which substantially increase the risk of CMV reactivation[9,13,14].

Before the registration of letermovir, the standard of care for management of CMV infection in HSCT had been regular surveillance of virological reactivation and pre-emptive therapy. Conventional antivirals used in the treatment of CMV infection were also used as prophylaxis in high risk patients[15–18]. While these agents are effective in the prevention of CMV reactivation, their use is associated with significant toxicity and has not been shown to be superior to the pre-emptive strategy.[19–21]. These approaches have reduced the burden of CMV disease and its associated morbidity and mortality[19,22]. However, the burden of CMV infection remains prominent, and pre-emptive therapy entails hospitalization, significant adverse effects, and considerable expenses[23,24]. In a single-institute study in the United States (US), pre-emptive therapy for CMV infection post-HSCT incurred an additional cost of US dollars (USD) 58,000–74,000 per patient for antiviral medication and longer hospital stays[23]. In another similar study, the cost of pre-emptive therapy for CMV infection was USD 116,976 per patient, compared with USD 12,496 per patient without CMV infection[25]. Besides the additional economic burden due to CMV infection and the need for pre-emptive therapy, higher mortality rates have been observed in allogenic HSCT patients with CMV viremia. In a cohort study, 962 allogenic HSCT patients underwent weekly polymerase chain reaction (PCR) testing of plasma for CMV monitoring through day 100 post-HSCT. The study results showed that the cumulative overall mortality was 30% (95% CI: 26.9–33.0) by one year post-HSCT. CMV viremia was associated with an increased risk of death even though patients received pre-emptive therapy when CMV viral load was detected at 125 IU/ml. Furthermore, CMV viral load of $\geq$250 IU/ml was associated with increased risk of early (0–60 days post-HSCT) death (adjusted HR 18.1, 95% CI: 8.8–37.4)[26].

Hence, the preferred strategy for management of CMV post-HSCT is not only to prevent clinical disease, but also virologic reactivation. A number of agents have been explored for prophylaxis of CMV reactivation in HSCT patients including letermovir, maribavir, and brincidofovir[3,27,28]. Letermovir is a novel CMV terminase inhibitor and is the only drug currently approved for prophylaxis of CMV reactivation in adult seropositive allogeneic HSCT recipients[3,29]. In a phase 3 study, letermovir prophylaxis reduced clinically significant CMV infection at 24 weeks post-HSCT with similar safety profile compared with placebo[3]. In line with previous reports suggesting an increased risk of overall mortality after HSCT with any level of CMV viremia[30], all-cause mortality was also found to be significantly reduced in letermovir recipients at 24 weeks post-HSCT.[3,26]. Subsequent analysis showed that the reduction in all-cause mortality is likely mediated by prevention of clinically significant CMV infection[31]. A recently published updated guideline for management of CMV infection in HSCT patients from the 2017 European Conference on Infections in Leukaemia (ECIL 7) strongly supports the recommendation for use of letermovir as antiviral prophylaxis after allogenic HSCT[32].

There are currently no published data on the cost-effectiveness of letermovir prophylaxis in any Asian country. We considered Hong Kong a suitable place for such an analysis. Its public healthcare is effectively a national health system, whereby cost-effectiveness considerations are important and unaffected by reimbursement policies. The current study aimed at evaluating the clinical impact and cost-effectiveness of letermovir as CMV prophylaxis in adult allogeneic HSCT recipients, compared with the conventional strategy of pre-emptive therapy without antiviral prophylaxis (pre-emptive strategy) from the perspective of a healthcare provider in Hong Kong. In both groups of patients, regular surveillance of CMV viraemia were performed and pre-emptive treatment would be given at signs of virological reactivation[3].

Methods

Cost-effectiveness model structure overview

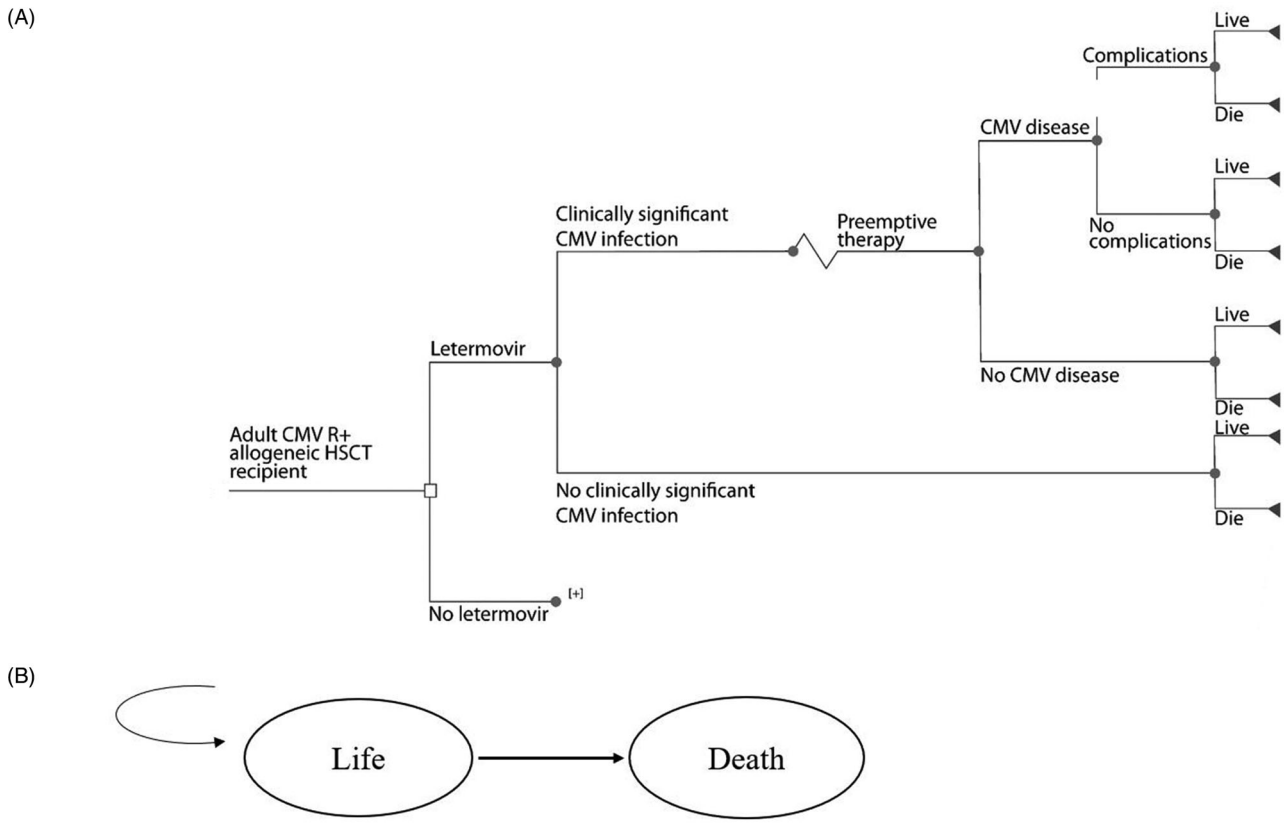
The cost-effectiveness model was designed to consider an analysis from the perspectives of a healthcare provider in Hong Kong, and included the total cost attributable to prophylaxis, pre-emptive therapy, CMV disease and related outcomes. The patient population for the model was derived from a reported letermovir clinical study[3,33].

Cost-effectiveness was assessed through a decision analytic model evaluating the progression of clinically significant CMV infection and related outcomes at week 14 (prophylaxis period) and week 24 (primary outcome assessment) (Figure 1). The model utilized data from the clinical study regarding the initiation of pre-emptive therapy, CMV disease, and other CMV-associated complications such as GVHD (Table 1)[33]. The decision tree was developed for the first 24 weeks post-HSCT, including the probability of developing clinically significant CMV infection followed by the administration of pre-emptive therapy and associated adverse events, the probability of developing CMV disease and other associated complications. For patients who are alive after 24 weeks, a Markov model was developed and long-term survival over a lifetime was extrapolated.

The model estimated relative differences in costs, life expectancy, quality-adjusted life years (QALYs), and clinical outcomes at 24 weeks for adult seropositive patients undergoing allogeneic HSCT. Costs and clinical benefits, expressed as QALYs, were discounted at 3% per year.

Clinical input used in the decision tree

The data on efficacy of letermovir prophylaxis in preventing clinically significant CMV infection and disease was derived from the letermovir phase 3 study[33]. Two arms were evaluated, the CMV prophylaxis or letermovir arm, and the pre-emptive strategy arm. Patients in the letermovir arm were administered letermovir orally or intravenously from day 0 to week 14 post-HSCT at a dose of 480 mg per day (or 240 mg



Abbreviation: CMV: cytomegalovirus; HSCT: hematopoietic stem cell transplant
Note: [+] indicates the pathway is same as above

Figure 1. Structure of the decision model. (A) Decision tree for the first 24 weeks. (B) Markov model used after 24 weeks.

Table 1. Clinical inputs, utility values and direct medical costs considered in 24 weeks analysis.

	Prophylaxis#	
	Letermovir	Nil
Clinical outcome		
Clinically significant CMV infection*	17.2%	42.4%
CMV disease	1.8%	2.1%
CMV related re-hospitalization	2.8%	7.6%
Graft-versus-host disease	49.8%	54.1%
All-cause mortality	10.2%	15.9%
Utility values		
Baseline	0.649	0.649
Week 14	0.756	0.674
Week 24	0.757	0.689
Post-trial	0.760	0.760
Items	Direct medical costs (HKD)	
Letermovir (per day)	1,690	
Pre-emptive therapy (inpatient) (per day)	6350.70	
Pre-emptive therapy (outpatient) (per day)	40	
CMV disease (total pre-emptive therapy cost)	89,469.80	
Total CMV related re-hospitalization	53,550.00	
Total GVHD treatment	45,456.25	
Pre-emptive therapy related adverse event)	11,242.00	

*Patients with clinically significant CMV infection are assumed to receive pre-emptive antiviral treatment. Abbreviations. CMV, cytomegalovirus; GVHD, graft-versus-host disease.
#In both group of patients, there is regular surveillance of virological reactivation and preemptive therapy will be given at signs of reactivation. Nil prophylaxis is equivalent to preemptive therapy alone (see text for details).

per day in patients with concomitant cyclosporine treatment). The mean age of the trial population at baseline was 50.8 years[34].

Both groups of patients received weekly CMV viral load monitoring, followed by the initiation of antivirals for pre-emptive therapy or treatment of CMV disease as needed[35]. The primary efficacy endpoint was the proportion of patients with clinically significant CMV infection through week 24 post-HSCT. Study patients were subsequently followed for an additional 24 weeks until study completion at week 48 post-HSCT; in order to ascertain CMV disease, health outcome data including incidence of all-cause mortality, re-hospitalizations (including those for CMV-related causes), GVHD, opportunistic infections, and quality of life measures using validated patient reported outcome tools[33]. Patients were assessed for outcomes regardless of whether they received pre-emptive therapy, thereby ensuring that all patients would be evaluated at any given time point. The incidences of neutropenia and adverse events related to pre-emptive therapy were considered equal to 12.5% as reported previously[35]. Life-years during the first 24 weeks were estimated from the mortality observed in the letermovir phase 3 study[33].

Long-term survival inputs

Life-years post 24 weeks were estimated for the 24-week survivors, applying the average adjusted annual relative risk of underlying cause of death post-HSCT (acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, chronic myeloid leukemia, severe aplastic anemia, chronic lymphocytic leukemia, plasma cell myeloma and myelofibrosis; severe

aplastic anemia considered similar to chronic myeloid leukemia/chronic lymphocytic leukemia; myelodysplastic syndrome considered similar to myelofibrosis and plasma cell myeloma)[30]. The relative risk of death at one-year post-HSCT was considered equal to the risk for the second-year post-HSCT for each underlying disease, accordingly until the fifteenth year[30]. Fifteen years post-HSCT, the relative risk for mortality was considered static, being the average risk from year 10 to 15[30].

Model parameters of utility values

Treatment-specific utility values were derived from the letermovir phase 3 study[3,33]. Utility values were based on EuroQol 5 dimensions (EQ-5D)-3L responses. The post-trial utility value was obtained from a UK societal-based study conducted in patients diagnosed with acute myeloid leukemia, who were cured functionally[36].

Model parameters of costs

Costs used in the model are presented in Table 1. The primary source of information was derived from current costs at the allogeneic HSCT unit at Queen Mary Hospital, the sole adult allogeneic HSCT center in Hong Kong. All costs were provided using local currency (1 HKD ≈ 0.13 USD).

Although the standard dose of letermovir is at 480 mg orally per day, an adjusted dose of 240 mg was considered for the model, because based on local clinical practice virtually all patients are placed on cyclosporine post-HSCT. The cost of prophylaxis was assumed to be Hong Kong dollar (HKD) 1,690 per day for a prophylaxis duration of 69.4 days[34]. For pre-emptive therapy, at a typical average weight of 60 kg for Hong Kong people, inpatient costs/day were HKD 1,662 for foscarnet (120 mg/kg/day), HKD 291 for ganciclovir (5 mg/kg/day), and HKD 5,100 for hospitalization; for a duration of 14 days. The cost for outpatient treatment per day was HKD 40 for valganciclovir (900 mg), for a duration of 14 days. The proportion of patients receiving foscarnet and ganciclovir in the inpatient setting was set at 70 and 30% respectively, based on real-life practice showing that foscarnet was used more frequently than ganciclovir, which caused cytopenia in the first 100 days post-HSCT. For adverse events associated with pre-emptive therapy, including neutropenia due to ganciclovir/valganciclovir treatment, the total cost of management including the use of granulocyte colony stimulating factor (G-CSF) was estimated to be HKD 11,242. This included the total cost of specialist visit, complete blood count, serum biochemistry, CMV detection assay, G-CSF treatment, and nurse injection fee. A mean hospital stay of 10.5 days was considered necessary for treatment of CMV-related disease, incurring a total cost of HKD 53,550.

For treatment of GVHD, methylprednisolone (MP) (2 mg/kg/day for 1 week, 1.5 mg/kg for 1 week, then complete tapering in 6 weeks) and mycophenolate mofetil (intravenously for 2 weeks, then orally for 6 weeks) would be administered, for a total cost of HKD 45,456.25. The further breakdown included total regimen cost for MP, regimen cost for mycophenolate mofetil, and hospitalization costs.

Sensitivity analysis

The model input parameters were varied individually in a one-way sensitivity analysis to examine their impact on the model results. Also, probabilistic sensitivity analysis was conducted to explore the impact of simultaneous variation of the model inputs on the subsequent results. Different probabilistic distributions were used such as beta distributions for clinical parameters and gamma distributions for economic parameters. In total, 10,000 iterations were simulated to perform the analysis.

Results

Base-case analysis: clinical outcome

Compared with the pre-emptive strategy, letermovir prophylaxis had higher expected life-years and QALYs with numerically fewer cases of clinically significant CMV infection, CMV disease, CMV-related hospitalizations, GVHD and treatment-associated neutropenic episodes (Table 2).

Base-case analysis: costs

The base-case results showed that in the lifetime analysis predicated on 24-week outcomes, letermovir prophylaxis strategy had a higher total cost due to the increased cost of CMV prophylaxis (Table 2). Costs were partially offset by increased use of CMV antivirals for pre-emptive therapy, CMV related re-hospitalization, CMV disease, GVHD, and pre-emptive therapy related neutropenia costs for patients in the pre-emptive strategy group (Table 2).

Base-case analysis: incremental cost-effectiveness

Incremental cost-effectiveness analysis showed that each life-year gained with letermovir prophylaxis had an associated cost of HKD 193,580 (∼25165 USD) and each QALY gained had an associated cost of HKD 234,675 (∼30508 USD) (Table 3), both of which fell below one gross domestic product (GDP) per capita for Hong Kong (HKD 382,046), the defined cost-effectiveness threshold within this study. Although letermovir prophylaxis resulted in fewer clinically significant CMV infections, CMV disease, CMV related hospitalizations, and GVHD, it is more costly than pre-emptive strategy (Table 3).

Sensitivity analysis: one-way sensitivity analysis

Results of the one-way sensitivity analysis are summarized in a tornado diagram (Figure 2). The one-way sensitivity analysis results showed that the base-case model results (in terms of the incremental cost-effectiveness ratio, ICER) were most sensitive to the inputs defining the mortality benefit: probability of all-cause mortality for pre-emptive strategy at 24 weeks, followed by the mean age of the patient population, and the all-cause mortality for letermovir at 24 weeks. Hence, the benefits of letermovir against all-cause mortality is one of the primary drivers of cost-effectiveness in the base-case scenario.

Table 2. Base case expected clinical outcomes and costs for a cohort of 100 people over a lifetime (based on 24 weeks) time horizon.

	Prophylaxis#		Difference	Relative difference (%)
	Letermovir	Nil		
Outcome				
Life-years	758.01	711.77	46.24	6.50
QALYs	576.46	538.32	38.14	7.09
Clinically significant CMV infection	17.20	42.40	−25.20	−59.43
CMV disease	1.80	2.10	−0.30	−14.29
CMV related re-hospitalizations	2.77	7.65	−4.88	−63.79
GvHD	49.85	54.12	−4.27	−7.89
Pre-emptive therapy related neutropenia	2.15	5.30	−3.15	−59.43
Cost (HKD)				
CMV prophylaxis	11,723,530	0	11,723,530	Undefined
Pre-emptive therapy	1,538,881	3,793,520	−2,254,639	−59.43
CMV disease	161,046	187,887	−26,841	−14.29
CMV related re-hospitalizations	148,292	409,500	−261,208	−63.79
GvHD	2,265,819	2,459,985	−194,166	−7.89
Pre-emptive therapy related neutropenia	24,170	59,583	−35,412	−59.43
Total	15,861,738	6,910,474	8,951,264	129.53

Abbreviations. CMV, cytomegalovirus; GvHD, graft-versus-host disease; HKD, Hong Kong dollar; QALYs, quality-adjusted life years.
#In both group of patients, there is regular surveillance of virological reactivation and preemptive therapy will be given at signs of reactivation. Nil prophylaxis is equivalent to preemptive therapy alone (see text for details).

Table 3. Incremental cost-effectiveness ratios for a cohort of 100 people over a lifetime (based on 24 weeks) time horizon.

ICER	Value (HKD)	Conclusion
Life-year gained	193,580	Letermovir prophylaxis improves life-years at an increased cost
QALY gained	234,675	Letermovir prophylaxis improves QALYs at an increased cost
Clinically significant CMV infection avoided	355,209	Letermovir prophylaxis reduces clinically significant CMV infections at an increased cost
CMV disease avoided	29,837,547	Letermovir prophylaxis reduces CMV disease at an increased cost
CMV related hospitalization avoided	1,835,092	Letermovir prophylaxis reduces CMV related re-hospitalizations at an increased cost
Graft-versus-host disease avoided	2,095,582	Letermovir prophylaxis reduces graft-versus-host disease at an increased cost
Pre-emptive therapy related AE avoided	2,841,671	Letermovir prophylaxis reduces pre-emptive therapy related AEs at an increased cost

Note: ICER should be interpreted as 'no prophylaxis' versus letermovir.
Abbreviations. AEs, adverse events; CMV, cytomegalovirus; HKD, Hong Kong dollar; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year gained.

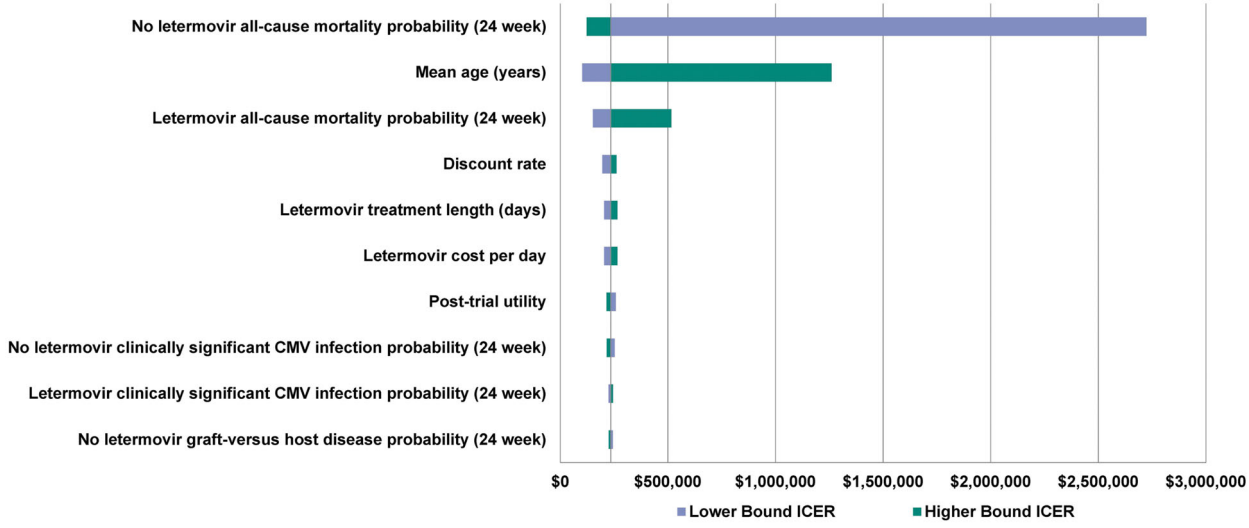


Figure 2. One-way sensitivity analysis for a cohort of 100 people over a lifetime horizon (based on 24-week outcomes). Tornado diagram for a cohort of 100 people over a lifetime (based on 24 week) time horizon. Abbreviations. CMV, cytomegalovirus; HKD, Hong Kong dollars; ICER, incremental cost-effectiveness ratio.

Sensitivity analysis: probabilistic sensitivity analysis

As shown in the cost-effectiveness acceptability curve results (Figure 3), letermovir prophylaxis is more cost-effective than "pre-emptive" strategy, and this statistic remains valid in 75.98% of the iterations. The scatter plot shows that the majority of the ICERs from iterations comparing letermovir prophylaxis with pre-emptive strategy fell below one GDP per capita at thresholds of HKD 382,046 per QALY gained. The dashed line showed the cost-effectiveness thresholds considered in the analysis (Figure 4).

Discussion

This is the first Asian study analyzing the cost-effectiveness of letermovir prophylaxis versus pre-emptive strategy in adult CMV-seropositive allogeneic HSCT recipients. In Hong

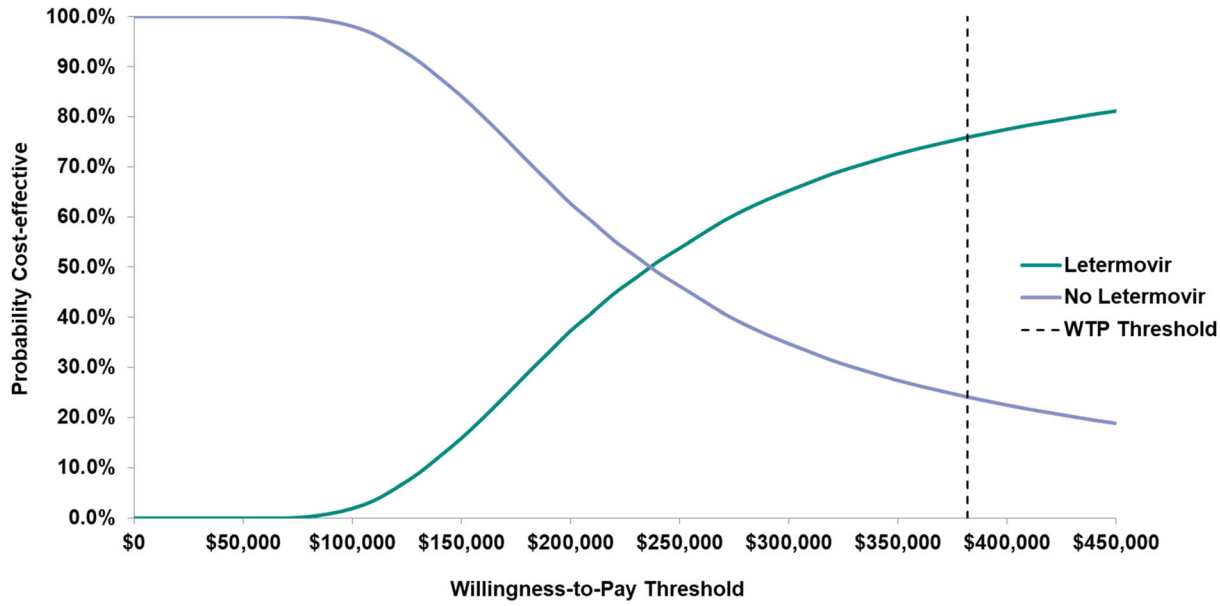


Figure 3. Cost-effectiveness acceptability curve for a cohort of 100 people over a lifetime horizon (based on 24-week outcomes). Abbreviations. WTP, willingness to pay; HKD, Hong Kong dollars.

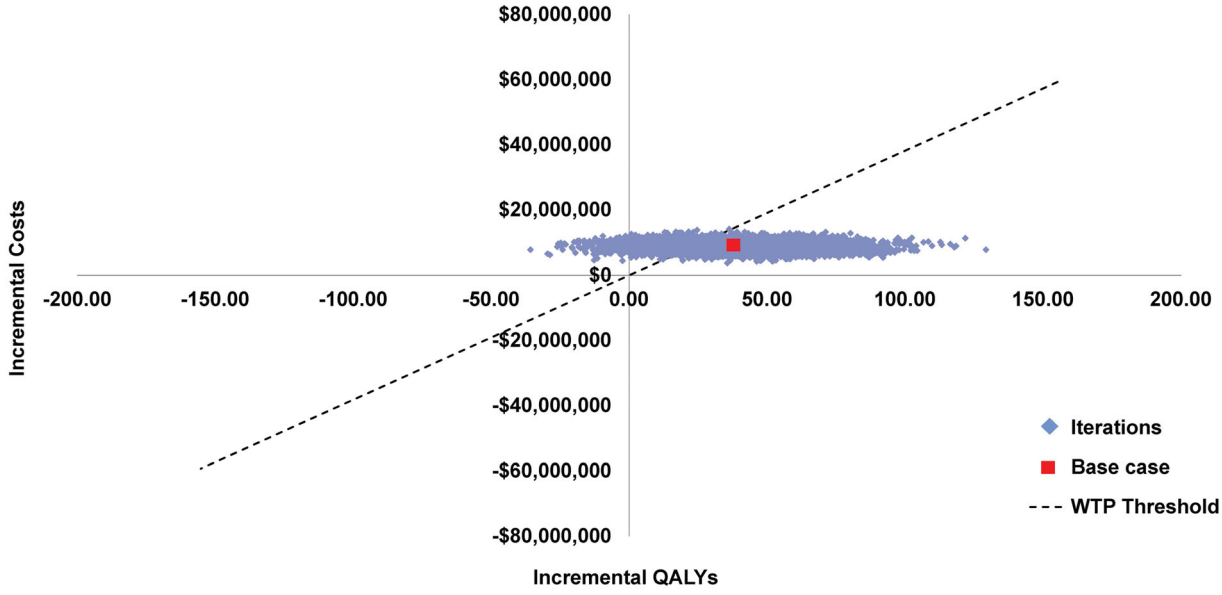


Figure 4. Probabilistic sensitivity analysis scatter plot (WTP = HKD 382,046; 10,000 iterations). Cost effectiveness scatter plot for a cohort of 100 people over a lifetime (based on 24-week) time horizon. Abbreviations. HKD, Hong Kong dollar; WTP, willingness to pay; QALY, quality adjusted life years.

Kong, the CMV seropositivity rate is around 90%[9], making it a clinically meaningful site for the analysis. The availability, efficacy and efficiency of its healthcare service are in the bracket of developed countries[37–39]. Furthermore, Queen Mary Hospital is the only adult allogeneic HSCT center in Hong Kong, so that bias due to patient selection would be obviated. This cost-effectiveness model can be used to explore the expected costs and outcomes for letermovir as CMV prophylaxis in adult seropositive HSCT recipients, compared with pre-emptive strategy in a variety of scenarios.

The results of the analysis showed that letermovir prophylaxis was associated with an increased cost as compared with the pre-emptive strategy. However, letermovir prophylaxis resulted in improvement in patient outcomes, as measured by life-year and QALYs gained. The increased cost of letermovir prophylaxis was partially offset by the decreased need and hence cost of pre-emptive therapy, re-hospitalization with CMV, clinical CMV disease, and GVHD. In a probabilistic sensitivity analysis, the majority of ICERs fell below one GDP per capita at thresholds of HKD 382,046 per QALY gained. Therefore, the use of letermovir for CMV prophylaxis is cost-effective in Hong Kong. Our results are in line with cost-effective analyses conducted in Italy[40], the United Kingdom[41], Portugal[42], and USA[43]. In a retrospective analysis of patients who underwent allogeneic HSCT, the letermovir prophylaxis cost was USD 23,270 for each life-year

gained and USD 25,222 for each QALYs gained. The results suggested that letermovir prophylaxis was associated with longer life and improved health-related quality of life[44]. In another cost-effective analysis, letermovir prophylaxis compared with pre-emptive strategy led to a mean increase of 0.45 QALYs, and an ICER of 22,564 Euros/QALYs, which was below the national ICER of 25,000–40,000 Euros/QALYs[40].

There has been a paucity of data regarding economic burden following CMV infection in Asia. A recent study used data from a Japanese hospital insurance claim database to compare the aggregate medical costs of patients who experienced CMV reactivation with those who did not[45]. The main differences between that study and ours are that we itemized specific agent-related costs for ganciclovir and foscarnet, and only included patients with confirmed CMV reactivation who met treatment criteria for pre-emptive therapy. The Japanese study reported higher medical costs than ours, which could be attributable to the incorporation of more components, including additional medications, blood products, and clinical examinations; which was in contrast to our study that only included the costs of antiviral agents, hospitalization, and treatment of GVHD. Furthermore, the economic implications of pre-emptive therapy for CMV infection, including blood tests, monitoring investigations, concomitant medications, opportunistic infections, and adverse events associated with treatment (leucopenia and thrombocytopenia), had not been taken into consideration. Had these factors been evaluated, the percentage difference between two groups would have been even more significant. Due to the limitation of currently available data, further prospective data are needed to address these costs. A further limitation of our study is that, as letermovir is an inhibitor of cytochrome p450(CYP) 3A enzyme and dependent on hepatic clearance, changes in drug exposure levels may occur in the presence of severe liver GVHD or significant drug-drug interactions. Further study would be useful to assess the applicability of this study on these patients.

In conclusion, the use of letermovir prophylaxis, compared with pre-emptive strategy, is a cost-effective option in adult CMV-seropositive recipients of allogenic HSCT from a healthcare provider perspective in Hong Kong.

Transparency

Declaration of funding

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Declaration of financial/other interests

The authors have no other financial interests to declare.

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Author contributions

TSYC and SSYC were the principal investigators for this study. TSYC and SSYC contributed to the study implementation and data collection. TSYC, YLK, WTC, DCH, RWYC, SHK, and SSYC contributed to the study design and implementation, data interpretation, drafting and editing of the manuscript. AA was primarily involved in model development and interpretation.

All authors contributed to the data interpretation, development, and review of this manuscript, and confirm that this report is consistent with established ethical standards of publication. The sponsor also provided a formal review of this manuscript.

All authors met ICMJE criteria and all those who fulfilled those criteria were listed as authors. All authors had access to the study data and made the final decision about where to publish these data and approved the submission.

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