BONE TARGETING AGENTS IN PREVENTION OF SKELETAL-RELATED EVENTS IN METASTATIC CANCERS OF SOLID TUMOURS: AN ECONOMIC EVALUATION

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Abstract: Skeletal related events (SREs) are skeletal complications from bone metastases such as spinal cord compression, pathological fracture, palliative radiation to the bone and bone surgery. These events resulted in greatest morbidity which affecting patients' quality of life over the years and may increase healthcare cost in treating SREs. Therefore, preventing SREs may reduce the economic burden to health care. Bone targeting agents (BTA) significantly delayed time-to-first SREs and reduced the risk of first and subsequent SREs in majority of cancers. Among all BTA, denosumab and zoledronic acid are the most effective and commonly used in preventing SREs. The objective of this evaluation was to assess the cost-effectiveness of BTA in prevention of SREs in metastatic cancer of solid tumours and its financial implication. The economic evaluation was designed from provider perspective (Ministry of Health, Malaysia) using literature-based Markov model to compare the costs and quality adjusted life years (QALY) for hypothetical cohort of patients with primary solid tumour with bone metastases. Based on the model, the use of BTA in preventing skeletal-related events among solid tumour patients with bone metastases is a cost-effective strategy. Within this evaluation, the most cost-effective option was 12-weekly intravenous Zoledronic acid, yielding an incremental cost-effectiveness ratio of RM 4,969 per QALY gained. The estimated total financial implication for this strategy was RM 8.8 million per year. In conclusion, 12-weekly Zoledronic acid is the most cost-effective option in preventing SREs in solid tumour cancer patients with bone metastasis.

Keywords: skeletal-related events, bone metastases, cost-effectiveness analysis, economic evaluations

Introduction

Bone is a frequent site of metastases, particularly in patients with multiple myeloma, and solid tumours such as breast, prostate, lung and renal cancer. By disrupting osteolysis and osteogenesis, bone metastases diminish bone integrity and hence, increasing the risk of skeletal-related events (SREs) which include pathological fracture, spinal cord compression, bone pain, hypercalcaemia of malignancy and the need for radiation or surgery to the bone (Carter JA *et al*, 2012). Skeletal-related events were found to be associated with reduction in patients' health-related quality of life, decrease in their survival, affecting the quality of life of the family or carers and incur financial burden to the patients as well as health care system (Puteh SEW *et al.*, 2013). Thus, the primary treatment goals in the management of bone metastasis include the prevention of SREs, the reduction of pain and the improvement in health-related quality of life (Carter JA *et al*, 2012).

Bone targeting agents such as biphosphonates and Denosumab has been used as treatment options for bone metastases. It can often shrink or slow the growth of bone metastases and prevent SREs, however, treatment is predominantly palliative (Andronis L *et al.*, 2018). In the United Kingdom, the National Institute for Health and Care Excellence or NICE (2011, 2009, 2008) recommended that biphosphonates can be offered to patients with lung cancer, advanced breast cancer and metastatic cancers with spinal cord compression. In Ministry of Health

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Malaysia Drug Formulary (2017), Ibandronic Acid tablet and Denosumab injection was approved for the treatment of post-menopausal osteoporosis, while Zoledronic Acid was approved for prevention of SREs only in patients with multiple myeloma involving multiple bone lesions. As these agents play an important role in preventing SREs in patients with metastatic solid tumours, their effectiveness and economic implications need to be evaluated.

Malaysian Health Technology Assessment Section (MaHTAS), Ministry of Health Malaysia conducted a health technology assessment on these bone targeting agents to evaluate the effectiveness, safety and cost-effectiveness when given to patients as prevention of SREs in patients with Stage IV cancers of solid tumours with bone metastases (Atikah S *et al*, 2018). From the review, it was found that bone targeting agents significantly delayed time-to-first SREs and reduced the risk of first and subsequent SREs in majority of cancers. Among all biphosphonates, Zoledronic Acid has the highest effectiveness in delaying first SREs in breast and lung cancer however, no significant difference in terms of treatment regime for Zoledronic Acid, whether given as intravenous injection 4-weekly or 12-weekly. When compared with Denosumab, it was found that Denosumab was superior than Zoledronic Acid in delaying the time to first SRE (HR=0.82, 95% CI 0.78, 0.87) and reducing the risk of first SRE (RR=0.83, 95% CI 0.77, 0.87).

In view of limited use of bone targeting agents in prevention of SREs among patients with metastatic cancers of solid tumours as outlined in Malaysian Ministry of Health Drug Formulary, this economic evaluation was conducted to add new indications of these agents. The general objective of this study was to assess the cost-effectiveness of bone targeting agents in prevention of SREs in metastatic cancer of solid tumours. The specific objectives were to calculate the incremental cost-effectiveness ratio (ICER) between Zoledronic Acid and Denosumab with current best supportive care in prevention of SREs and to estimate the budget impact and financial implications when patients with bone metastases secondary to solid tumours transitioned from usual care (no prophylaxis) to bone targeting agent as SRE prophylaxis.

Methodology

A literature-based state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2007 to estimate the lifetime costs and quality adjusted life years (QALYs) of using bone targeting agents as prevention of SREs in patients with bone metastases secondary to solid tumours. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials in metastatic solid tumours to longer term cost-effectiveness results. A hypothetical cohort of 1000 stage IV cancer patients with bone metastases were simulated in three strategies:-

i) usual care / best supportive care (no bone targeting agents given)

ii) 12-weekly intravenous Zoledronic Acid 4mg

iii) 4-weekly subcutaneous Denosumab 120mg

Model Structure

The model structure was constructed with reference to other published studies (Carter JA et al, 2011, Xie J et al, 2011, Botteman M et al, 2007) and in consultation with expert committees consist of multidisciplinary experts namely clinical oncologists, orthopaedic oncologist, health economists, public health physicians and pharmacists. In general, this Markov model included seven health states in two disease conditions, namely stable metastatic and progressive metastatic disease, with dead as the absorption state (Figure 1).
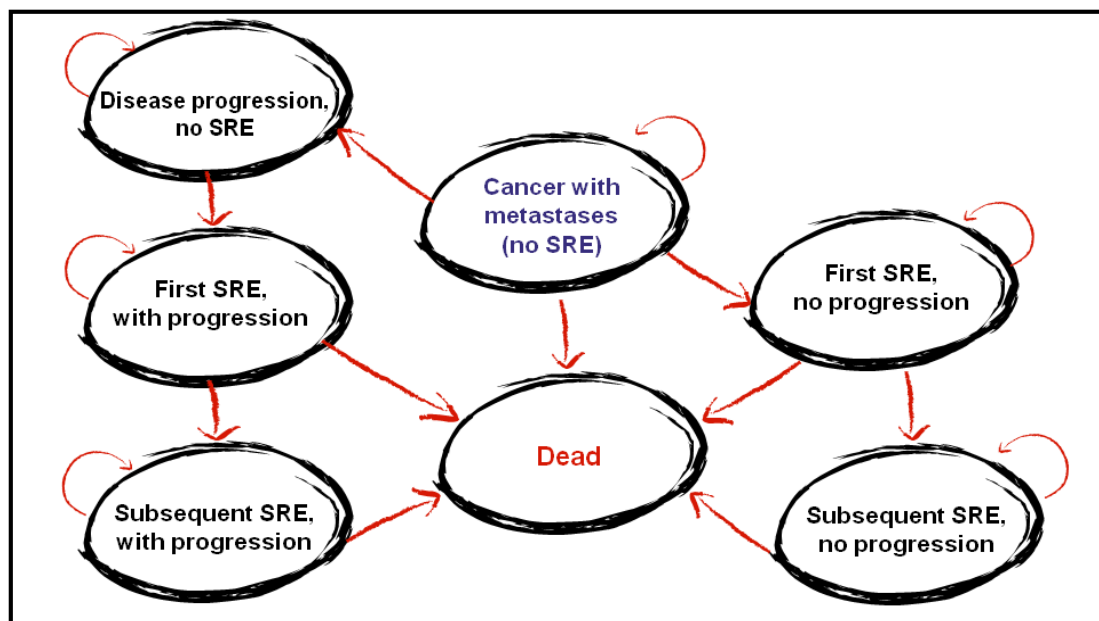
Figure 1: Markov model of bone targeting agents versus usual care in prevention of skeletal-related events.

The simulated clinical pathways are as follow:

- Patients entered the model in the post-diagnosis state after confirming presence of bone metastases and without SRE (cancer with metastases, no SRE). In the usual care / best supportive care cohort, no bone targeting agent was given in preventing SRE and all patients were managed according to standard care.

- In the cohorts of patients receiving bone targeting agent, 12-weekly intravenous Zoledronic Acid 4mg or 4-weekly subcutaneous Denosumab 120mg were given as prevention of SRE once the patients confirmed as Stage IV cancer with bone metastases. Once patient developed SRE, the same bone targeting agent was given as treatment. Calcium supplementation was also given to patients who received bone targeting agents.

- Patients would either remain in stable metastatic disease (without progression) or having disease progression before experiencing the first episode of SRE and/or subsequent SRE.

- The health outcome and economic impact related to drug-induced severe adverse events were not included in the model due to its rarity (<1%) (Botteman M et al, 2006)

- In patients receiving Zoledronic Acid, renal monitoring test was performed prior to each treatment in view of possible complication of renal toxicity (Xie J et al, 2011)

- All patients received palliative care and follow-up in oncology specialists clinic was 3-monthly.

- Death was only possible due to metastatic cancer and not other causes.

- The model decision analyses were projected to lifetime horizon (84 months) and the transition cycle was quarter year or equal to 13 weeks.

Assumptions

It is a common approach to use assumptions based on available published literature or expert consultations in economic modelling. The following key assumptions were used in this model:

- The same bone targeting agent is given as prevention and treatment of SRE in the cohort (no switch of treatment once patient has SRE).

- The quality of life benefits (utility) of all bone targeting agents were assumed to be similar.

- Utility values in disease progression states are lower than in stable metastases.

- No more than one SRE could occur within each cycle, making the maximum SRE that may occur in a year is four times.

- The type of subsequent SRE was not dependent on the first SRE.

- Stable and progressive metastases states incur the same cost.

- Average cost of SRE-related treatments is the same regardless whether it is first SRE or subsequent SRE.

- Skeletal-related events did not change the mortality rate.

Model Estimation

The epidemiological and disease-related data were obtained from local sources of data whenever available, or literature review when local data was not available.

a.   Effectiveness Data and Transitional Probabilities

The effectiveness parameters in this study were obtained from published clinical trials as shown in Table 1. The main outcomes from these clinical trials were median time to first SRE and skeletal morbidity rate. No significant difference in overall survival and progression-free survival (Fizazi K et al, 2011, Saad F et al, 2004) hence, these two parameters were not included in this model.

Transitional probabilities among different states were derived primarily from the efficacy results of the phase 3 clinical trial comparing Denosumab and Zoledronic Acid which being used in an economic evaluation by Xie J et al (2011). Probabilities for usual care arm were obtained from a clinical trial comparing Zoledronic Acid and placebo (Saad F et al, 2004), which then utilised in an economic evaluation by Carter (2011).

Table 1 :Effectiveness data and transitional probabilities

Parameter	Usual care	Zoledronic Acid	Denosumab	Source
Median time to first SRE in months (SD)	11 (0.8)	17.1 (1.1)	20.7 (1.6)	Carter JA, 2011 Fizazi K, 2011 Xie J, 2011 Saad F, 2004
Skeletal morbidity rate	3.05	1.71	1.20	Xie J, 2011 Botteman M, 2006
Risk of hypocalcaemia	-	6%	13%	Fizazi K, 2011

Increased risk of having SRE and subsequent SRE due to progression	2.14	2.14	2.14	Xie J, 2011
Transitional probabilities				
From stable metastases to disease progression	0.221	0.221	0.221	Xie J, 2011
First SRE among patients without progression	0.245	0.115	0.096	Carter JA, 2011 Xie J, 2011
Subsequent SRE among patients without progression	0.355	0.167	0.137	Carter JA, 2011 Xie J, 2011
From any health states to death / absorption state	0.271	0.271	0.271	Xie J, 2011

*SD = standard deviation; SRE = skeletal related events

b. Utility Data

Utilities for the health states represented in the model were obtained from a time trade-off (TTO) exercise by Dranitsaris and Hsu (1999), which was the only published empirically-based estimate of utilities for bone targeting agents and SRE for patients with advanced breast cancer receiving Pamidronate, a type of biphosphonates. These utility values were incorporated in other published economic evaluations related to prevention and treatment of SRE in Stage IV cancers with bone metastases (Ford J et al, 2013, Botteman M et al, 2006). Hence, the same utilities were used in patients receiving any type of bone targeting agents. These values were compared with the utility value from ACTION study which was a longitudinal study on health-related quality of life among cancer survivors in Southeast Asia including Malaysia (ACTION Study, 2017). Utility for progressive disease was obtained from another health-state utilities study on metastatic breast cancer patients (Nafees B et al, 2016). All the utility values incorporated in the model were as shown in Table 2.

Table 2 :Utility inputs

Health states	Base case value	95% CI	Source
No SRE, receive BTA	0.64	0.53 - 0.76	Ford J, 2013 Botteman M, 2016 Dranitsaris G, 1999
No SRE, receive usual care	0.56	0.45 – 0.68	
SRE, receive BTA	0.46	0.37 – 0.54	
SRE, receive usual care	0.31	0.23 – 0.38	
Stage IV (progressive)	0.39	0.33 – 0.45	Nafees B, 2016
Stage IV (at diagnosis/stable)	0.65	SD = 0.24	ACTION Study, 2017

c. Resources and Cost Data

The costs used in this analysis were based on MOH Consumer Price Guide from Pharmaceutical Services Program (2018), Malaysian DRG Casemix costing (severity illness 2), MOH Investigation Charges from website (2018), published literature using local data (Lee WC et al, 2016, Zainal R et al, 2014, Dranitsaris G et al, 2011, Hwa YS et al, 2011) and personal communication with pharmacists from National Cancer Institute, Malaysia. Direct medical costs included were cost of drugs, cost of procedures such as IV and subcutaneous administration of drugs, cost of investigations such as renal profile, cost of SRE related management (pathological fracture, radiotherapy to the bone and spinal cord compression requiring instrumentation), cost of specialist clinic follow-ups and palliative care. All costs are expressed in Malaysian Ringgit (RM) and adjusted

accordingly to costs of the year 2017. For the drugs, the most recent costs in 2018 were used in the model. All the parameters for cost inputs are presented in Table 3. All results were presented as incremental cost-effectiveness ratio (ICER).

Table 3 : Cost parameters

Cost description	Base case estimate	Source
Tablet calcium carbonate 500mg (per month)	RM 180.00	MOH Consumer Price Guide (2018)
Renal profile (per test)	RM 5.00 (third class charge)	MOH Investigation Charges (2018)
Total cost IV Zoledronic Acid 4mg (per dose)	RM 472.00	National Cancer Institute Lee WC, 2016
Total cost SC Denosumab 120mg (per dose)	RM 1,239.14	National Cancer Institute Lee WC, 2016
Stable/progressive Stage IV disease (per year)	RM 21,830.77	MalaysianDRG 2018 (severity illness 2) Zainal R, 2014 Dranitsaris G, 2011
Average cost of first SRE related treatment	RM 5,132.04	MalaysianDRG 2018 (severity illness 2) Hwa YS, 2011

*IV = intravenous; SC = subcutaneous

Sensitivity analysis

Deterministic sensitivity analysis was performed as one-way sensitivity analysis to evaluate the impact of variations in key model inputs on the model results. Input parameters were varied over a specified range, standard deviation or using values of reported upper and lower limit of 95% confidence interval. Input parameters tested in sensitivity analyses were:

- annual discounting rate (0-5%)

- transition probability of subsequent SRE among patients without progression in Zoledronic Acid group (per cycle)

- utility values for usual care and Zoledronic Acid groups

- cost of first SRE-related managements (range: RM 1,845 to RM 8,745)

- cost of stable/progressive Stage IV disease (range: RM 17,710 to RM 31,552)

Results

Base-Case Analysis

The results of this Markov model reflected the incremental cost-effectiveness ratios if bone targeting agents (12-weekly Zoledronic Acid and 4-weekly Denosumab) were used as prophylaxis in prevention of skeletal related events in Stage IV solid tumours patients with bone metastases. The base case results of the evaluated strategies

were presented in Table 4. The mean total discounted cost and QALY per patient receiving 12-weekly zoledronic acid was RM 37,314.89 and 2.5836 respectively, while for 4-weekly denosumab was RM 57,231.09 and 2.7582. For usual care group in which no prophylaxis was given, the mean discounted cost and QALY was RM 32,544.36 and 1.6235 respectively.

Table 4: Incremental cost-effectiveness ratios (ICERs) for base-case

Strategies	Total cost per patient	Total QALY per patient	Incremental cost	Incremental QALY	ICER (compared to usual care)
Usual care	RM 32,544.36	1.6235	-	-	-
Zoledronic Acid	RM 37,314.89	2.5836	RM 4,770.53	0.9601	RM 4968.87
Denosumab	RM 57,231.09	2.7582	RM 24,686.73	1.1348	RM 21,754.66

The base case analysis indicated that the deterministic ICER for 12-weekly Zoledronic Acid was RM 4,968.87 per QALY gained. Over the lifetime of the patients cohort (approximately 7 years), there was a marginal cost increase of RM 4,770.53 and a marginal benefit of 0.9601 QALYs per patient when 12-weekly Zoledronic Acid was given as prevention of SRE in Stage IV solid tumour patients with bone metastases compared with no prophylaxis. The ICER for 4-weekly Denosumab was RM 21,754.66 with slightly higher incremental QALY gained of 1.1348 compared with Zoledronic Acid. Both ICERs were below the cost-effectiveness threshold of one gross domestic product (GDP) per capita per QALY gained for Malaysia.

However, 12-weekly Zoledronic Acid was the most cost-effective option with lower ICER compared with Denosumab. If generic Zoledronic Acid is to be used, whereby the price of this generic is lower than the originator drug by 60%, the estimated ICER is RM 3,718.01. This estimate was based on an assumption that the generic drug and the originator drug is of the same effectiveness.

Sensitivity Analysis

One-way sensitivity analysis was performed around key model parameters including discounting rate, clinical parameters, utility parameters as well as cost parameters for usual care and 12-weekly zoledronic acid cohorts. The findings from the analysis were presented in Table 5 and plotted as tornado diagram (Figure 2) to illustrate the differences in ICERs obtained given the range of parameter estimates being tested.

Table 5 : Sensitivity analysis of key model parameters (usual care vs Zoledronic Acid)

Parameters	95% CI limit / Range / Standard Deviation	ICER of lower value input	ICER of higher value input
Annual discounting rate	0% - 5%	RM 5,174.74	RM 4,600.12
Transition probability of subsequent SRE in patients without progression (ZA)	SD = 0.019	RM 5,026.56	RM 4,915.89
Utility values for usual care and ZA groups	Refer to Table 3	RM 6,131.09	RM 4,681.52
Cost of first SRE-related managements	RM 1,845 – RM 8,745	RM 4,478.36	RM 5,273.47
Total cost of stable and progressive Stage IV disease	RM 17,710 – RM 31,552	RM 3,834.01	RM 6,858.80

*CI = confidence interval; ICER = incremental cost-effectiveness ratio; ZA = Zoledronic Acid

By varying the input parameters, the estimated ICERs ranged from a lower bound of RM 3,834.01 per QALY gained to an upper bound of RM 6,858.80 when comparing usual care or best supportive care to prophylaxis Zoledronic Acid. All the ICERs generated were lower than one GDP per capita per QALY gained.
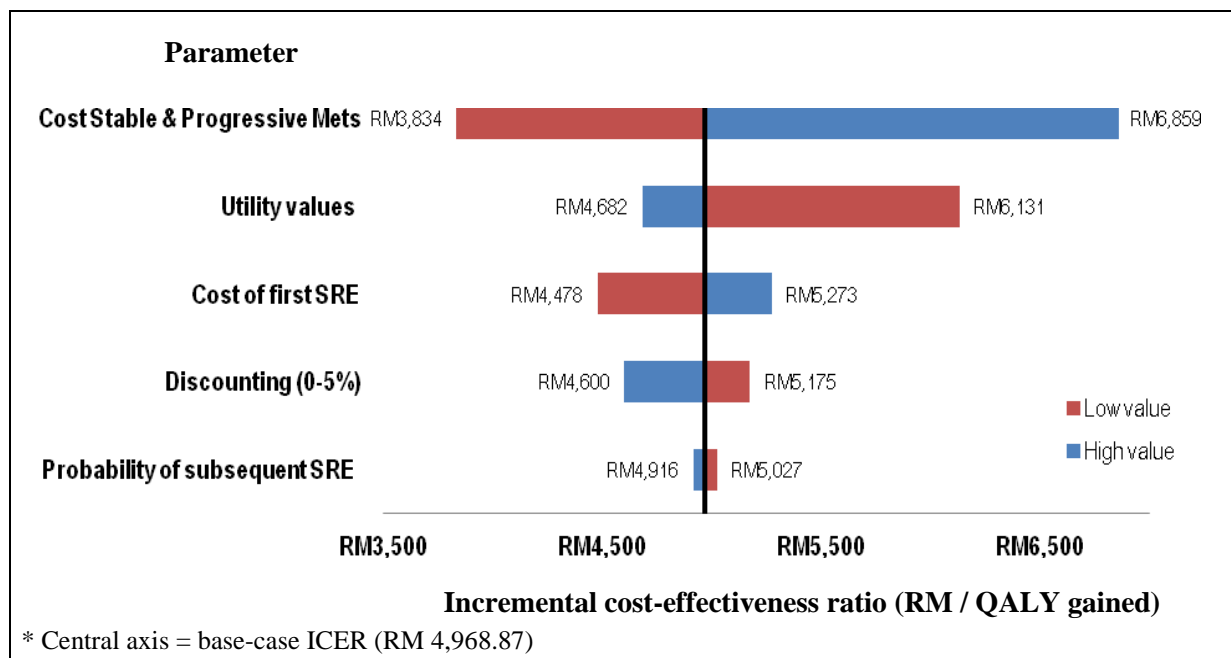

Parameter

* Central axis = base-case ICER (RM 4,968.87)

Figure 2 : Tornado diagram Zoledronic Acid (one-way sensitivity analysis)

From the sensitivity analysis, the most sensitive input parameter in this model was the total cost of management for stable and progressive Stage IV disease with bone metastases (**Figure 2**). Utility values, cost of first SRE-related management and discounting rate had moderate impact on the ICER as shown in the tornado diagram. In contrast, the result was not sensitive to different transition probability values of subsequent SRE in these patients.

Budget Impact Analysis / Financial Implication

This analysis will assess the cost implications per patient, per year and to predict the potential annual budget impact when patients with bone metastases secondary to solid tumours at risk of SRE are transitioned from usual care with no SRE prophylaxis to 12-weekly Zoledronic Acid.

It is estimated that approximately 70% of patients with breast or prostate cancer are affected by metastatic disease to the bone (Andronis L *et al*, 2018, Coleman RE, 2006) although no reliable incidence or prevalence figures were available for Malaysian population. From Malaysian National Cancer Registry Report (2007-2011), the total number of Stage IV patients among 13 solid tumour cancers was 14,671 and the average number of Stage IV patients per year was 2,934 (Zainal Ariffin O *et al*, 2011) Hence, approximately 2,054 patients with Stage IV solid tumours in Malaysia are affected by metastatic disease to the bone each year for these 13 type of cancers, assuming that the number of patients per year did not differ significantly.

Intravenous Zoledronic Acid 12-weekly as SRE prophylaxis incurred a total cost of RM 4,289.82 per patient per year for the drug and its administration / management while a 4-weekly strategy of the same drug would incur RM 9,081.90 per patient per year. Comparing these two strategies, 12-weekly prophylaxis would generate 52.77% cost saving per patient per year. If all patients with Stage IV solid tumour with bone metastases are given 12-weekly Zoledronic Acid, the total financial implication per year was approximately RM 8.8 million. If

4-weekly strategy was to be given to the same number of patients, the total financial implication per year was estimated to be RM 18.7 million.

Scenario Analysis

The total annual budget implications for patients transition from usual care to prophylactic Zoledronic Acid depends on the actual transition rate strategy by the stakeholders. **Table 6** outlined the total annual budget implications following transition of patients by 20% each year from usual care to 12-weekly Zoledronic Acid.

Table 6: Annual budget implications of transition from usual care to 12-weekly Zoledronic Acid by percentage of patients

Year (% of patients)	Year 1 (20%)	Year 2 (40%)	Year 3 (60%)	Year 4 (80%)	Year 5 (100%)
Budget implications	RM 1.7 million	RM 3.5 million	RM 5.3 million	RM 7.0 million	RM 8.8 million

Five most common types of primary cancer that metastasise to the bone are prostate, breast, lung, renal and thyroid cancer (Coleman RE, 1997). If the strategy is to offer 12-weekly Zoledronic Acid SRE-prophylaxis to these patients first before widening the coverage to all Stage IV patients with bone metastases, the budget needed was estimated to be RM 4.6 million.

Figure 3 illustrates the total budget implications following transition from usual care (no prophylaxis) to different strategies of SRE-prophylaxis with Zoledronic Acid by phases from 20% coverage to 100% coverage of patients. By using 12-weekly Zoledronic Acid compared with 4-weekly strategy, the predicted total cost-savings for every 20% patient transitions ranged from RM 2.0 million to RM 9.8 million. However, a more cost-saving impact would be achieved if 12-weekly generic drug of Zoledronic Acid is to be used as SRE-prophylaxis in Stage IV solid tumour patients with bone metastases (from RM 394,356.00 to RM 2.0 million).

The estimated benefit cost ratio if IV Zoledronic Acid is given for prevention of SRE compared to usual care is greater than one, which indicates that the benefits outweigh its costs. By using originator Zoledronic Acid, for every RM 1.00 spent, the cost-saving from SRE-related treatment is RM 1.50 while the saving is greater (RM 2.00) if generic Zoledronic Acid is used.
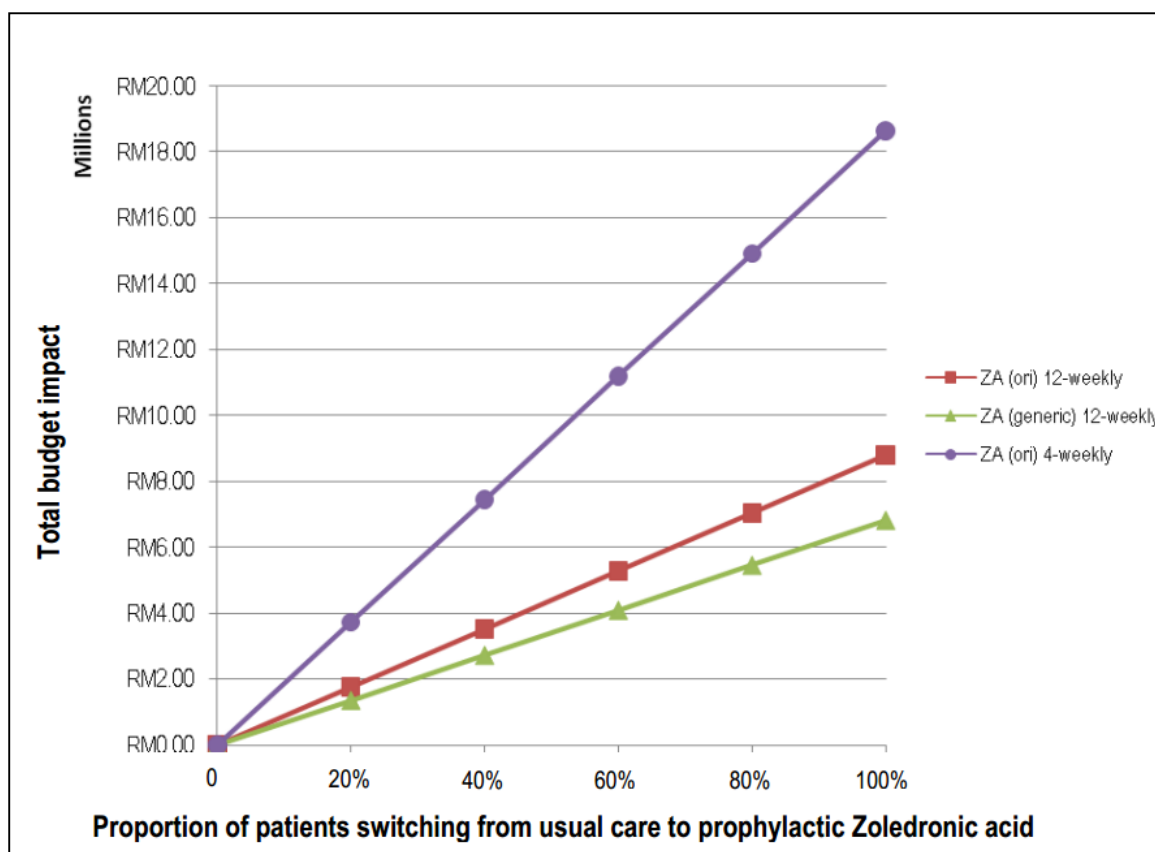
Figure 3 : Total budget implications following transition from usual care to different strategies of SRE-prophylaxis with intravenous Zoledronic Acid

Discussion

Bone targeting agents significantly delayed time to first SREs, reduced the risk of first and subsequent SREs in all types of cancer except non-small cell lung cancer. Denosumab was superior in reducing the risk of developing SREs, followed by Zoledronic Acid (Atikah S et al, 2018). The evidence on economic evaluation conducted in other countries suggested that Denosumab was the most effective intervention compared with Zoledronic Acid, however, it was associated with higher cost across all types of cancers (Atikah S et al, 2018).

The findings from our economic evaluation was consistent with other published studies (Ford J et al, 2013, Xie J et al, 2011, Botteman M et al, 2006). Although both Zoledronic Acid and Denosumab were found to be cost-effective interventions in preventing SREs, the most cost-effective option was using Zoledronic Acid. Among the main contributing factors for these findings were higher cost for Denosumab and limited evidence on the effectiveness of 12-weekly Denosumab in this group of patients for the given indication. Hence, Denosumab can only be given as 4-weekly regime compared with Zoledronic Acid, which can be prescribed 12-weekly.

Limitations

One of the main limitations of these analyses was the use of trial-based clinical parameters (SRE rates, transition probability, utility values) obtained from the literature review due to lack of real-world local data. These parameters could diverge from the national reality in absolute terms and hence, the final outcomes i.e. ICER could be under- or overestimated.

Another potential limitation is an assumption that was applied in estimating the cost of stable and progressive disease. Various cost estimates were available for management of malignancy-related condition in case-mix data or Malaysian DRG, depending on the types of cancer. Since most of the literatures evaluated the effect of SRE-

prophylaxis on breast and prostate cancer, malignancy-related costs from Malaysian DRG were taken from these two groups of patients. These limitations, however, were dealt through variation in the sensitivity analyses. In this decision analytic model, the cost of severe adverse events related to bone targeting agents were not included in the analysis due to its infrequent occurrence (<1%). However, if the costs of any of these severe adverse events (such as osteonecrosis of the jaw and severe hypocalcaemia) were taken into consideration, the total cost for bone targeting agents would be higher.

For budget impact and financial implication analyses, the data for number of Stage IV solid tumour patients were obtained from Malaysian National Cancer Registry Report 2007-2011. This report was outdated, given the latest year of patient registry was in 2011. The most recent registry that reported patients from year 2012-2016 is still in analysis phase and hence, could not be utilised for this economic evaluation. The most striking limitation in this registry report was low number of established reported stage of cancers. The percentages of recorded stage in this report ranged from 35% to 65% for the 13 solid tumours; hence, the budget analysis estimates could be higher than the calculated amount.

Conclusion

Based on this decision analytic model, the use of bone targeting agents in preventing skeletal-related events among Stage IV solid tumour patients with bone metastases is a cost-effective strategy from Malaysian healthcare provider perspective. Within this evaluation, the most cost-effective option was 12-weekly intravenous Zoledronic Acid, yielding an ICER of RM 4,968.87 per QALY gained which is lower than the cost-effectiveness threshold of 1 GDP per capita per QALY gained. The estimated total financial implications for this strategy with 100% potential patients' coverage was RM 8.8 million per year.

Acknowledgement

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