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ORIGINAL RESEARCH

Cost-effectiveness analysis of treating transplant-eligible multiple myeloma patients in Macedonia

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Purpose: A decision-analytic model was developed to study the impact of induction regimens vincristine, adriamycin, dexamethasone (VAD); thalidomide, dexamethasone (TD); and bortezomib, dexamethasone (BorD), followed by autologous stem cell transplantation (ASCT) for treating multiple myeloma (MM) patients in Macedonia. Additionally, a cost-effectiveness analysis (CEA) of treatment sequences to predict health effects and costs of different treatment sequences was performed.

Methods: Model strategies were based on a previously published study for treating patients with MM in Macedonia. The data on disease progression and treatment effectiveness were obtained from the published reports of randomized clinical trials (GIMEMA M-B02005, IFM 2005-01). Utility parameters were extracted from the literature. To compare treatment combinations, a decision tree model was developed. Additionally, a cost analysis for one-time per-protocol costs was performed from a Macedonian national health care perspective. The incremental cost-effectiveness ratios (ICERs)/quality-adjusted life years (QALYs) gained for 1-, 10-, and 20-year time horizons were determined. Costs and health outcomes were discounted to evaluate the effects of time in the model.

Results: The one-time costs of BorD (EUR 5,656) were higher compared to VAD (EUR 303) and TD (EUR 329), increasing the overall costs for BorD. Thus, the BorD combination dominated in the baseline results (1 and 10 years) and the ICER for TD vs. VAD was EUR 7,564/QALY (20 years, undiscounted model). However, in the discounted 20-year model, BorD showed an ICER of EUR 138,747/QALY gained for BorD vs. TD.

Conclusion: The CEA performed indicated that considering 1-year time horizon costs, VAD may be a cost-effective alternative vs. TD or BorD. However, for the longer period (10 or 20 years) including the discounting of future costs and outcomes, the TD and BorD combinations showed higher health benefits in terms of QALYs and more cost-effective vs. VAD. These results should be considered as supportive evidence by decision-makers and providers when deciding on the most cost-effective induction treatment strategy prior to ASCT in MM patients.

Keywords: decision-analytic modeling, decision tree, multiple myeloma, incremental cost-effectiveness ratio, transplant-eligible

Plain language summary

In the literature there is no published relevant cost-effectiveness analysis that compares different treatment sequence prior to autologous stem cell transplantation (ASCT) in multiple myeloma (MM), specifically for Macedonia. However, several randomized clinical trials that report the effectiveness of treating MM patients with induction treatment sequences prior to ASCT are known and published. With the aim to be able to combine those effectiveness results with the real-world costs data from Macedonia the aim of this research was to develop a decision tree

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model that could systematically evaluate and compare the expected outcomes of all alternative sequences prior to ASCT in MM patients in Macedonia, by simultaneously considering their benefits and costs. Furthermore, the goal was to assess the cost-effectiveness of the compared strategies beyond the time horizon used in the clinical trials with modeling techniques. Overall, the aim of this research work was to provide National Macedonian authorities and decision makers with supportive evidence on the relative effectiveness and incremental cost-effectiveness of induction treatment combinations prior to ASCT in MM patients.

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder worldwide known as 1% of overall cancer diagnoses and around 13% of all hematologic malignancies.[1–3] In Macedonia, the annual incidence rate is 0.8 for females and 1.2 for males per 100,000 population.[4,5] The disease has a very characteristic clinical picture, such as lytic bone disease, renal insufficiency, anemia, hypercalcemia, the presence of M-proteins found in the serum and/or urine, and immunodeficiency.[6–9] MM is known as a noncurable disease and the aim of therapy is to prolong survival and to improve patient quality of life. Moreover, in the last decade when novel therapies were introduced (bortezomib, thalidomide, and lenalidomide), the survival of MM patients improved; moreover, improvements were marked when using the novel agents as induction therapy prior to autologous stem cell transplantation (ASCT).[7–14] Using these agents, the rate of the complete response increased, thus prolonging the overall survival where the 10-year survival rate increased to ~30% with an improvement in the quality of life.[14] From the available evidence, it can be assumed that a patient who is newly diagnosed with MM nowadays is expected to live for an average of 5–7 years, with some exceptions where patients can live longer than 10 years.[4,5]

The initial therapy for transplant-eligible MM patients consists of 3–6 cycles of high-dose induction therapy followed by ASCT. The high-dose chemotherapy usually is a combination of two or more drugs consisting of dexamethasone combined with one or more novel agents (ie, bortezomib, thalidomide, and/or lenalidomide).[7,9,15] Stem cell transplantation can be either autologous or allogeneic and is administered as either a single or double (ie, tandem) transplantation. In Macedonia, in the period between 2000 and 2010 as published in an observational study, MM patients based on their eligibility for ASCT were treated with several combinations of drugs as induction therapy prior to stem cell transplantation.[13]

Due to the advanced therapeutic combinations and standard use of ASCT, the costs of care for MM increased in the last 20 years. The diagnosis in the older population (usually over 60 years of age) is also considered to have an impact on increasing the overall budget of MM treatment and thus affecting the overall health care budget in Macedonia. The cost of novel agent combinations and their usage as induction therapy prior to ASCT is substantially higher compared to the conventional chemotherapies that were used to treat MM patients prior to the new novel agents. The costs vary per treatment sequence and depend on the dose per cycle and number of cycles administered. Additionally, one should always notice the variation of drug prices over different countries as a result of different pricing regulations and the availability of generics in the market of the specific country.

Before authorizing funding and reimbursement of a new drug, decision-makers and health policy workers should recommend and require analyses of the comparative effectiveness and cost-effectiveness of both alternatives, new and old, thus creating a landscape of evidence where it could be observed what are the costs and benefits of each alternative, as well as harms. To our knowledge, there is no published cost-effectiveness analysis (CEA) for treating transplant-eligible MM patients, including the induction therapy prior to ASCT, for Macedonia. More explicitly, the aim of this study was to design a decision-analytic model that will evaluate the cost-effectiveness of three different induction regimens (vincristine, adriamycin, dexamethasone [VAD]; thalidomide, dexamethasone [TD]; and bortezomib, dexamethasone [BorD]) followed by ASCT (including tandem transplantations) for treating MM transplant-eligible patients in Macedonia.

Methods

Model structure and target population

The model structure for the decision tree was based on the treatment strategies of an observational study undertaken by the University Hematology Clinic in Skopje. In the study, 31 transplant-eligible MM patients were involved for the period 2000–2010.[13] Additionally, all further details on treatment patterns and management of the disease, in general, were discussed with clinicians. In Stojanoski et al's study,[13] 35 high-dose chemotherapy and ASCTs (including also 4 tandem transplantations) from peripheral blood stem cells were performed in the follow-up period of 10 years in 31 patients diagnosed with MM. All patients were treated with induction therapy in order to reach remission at the hospital using various chemotherapeutic combination regimens. The standard induction chemotherapy regimen was VAD, which was administered in 4 cycles every 28 days. Nonresponders received TD as a second-line therapy for a 5-month period. Furthermore, as a third-line therapy was used bortezomib.

The developed model was based on a decision tree analytical framework to compare VAD, TD, and BorD treatment alternatives prior to ASCT (including the tandem transplantation). The model employed a simple decision tree architecture that integrated the relevant VAD, TD, and BorD information for effectiveness and quality of life data from the previously published pivotal clinical trials and literature. The analysis framework was built under the assumption that a patient received one of the treatment combinations (VAD, TD, or BorD), as a first-line treatment regimen (induction therapy), following a complete response and continuing further with ASCT (if the disease was progressing a tandem transplantation was administered). The patients who did not respond to the induction regimen with VAD were redirected to the second-line treatment with TD. Furthermore, nonresponders with VAD and/or TD were assumed to continue their treatment with the third-line treatment[16] or further lines until they were eligible for ASCT. As Moureau et al[7] reported that the bortezomib, thalidomide, and dexamethasone combination is superior to TD or BorD combinations prior to ASCT, we decided to use as the further-line treatment for our decision tree model the bortezomib, thalidomide, and dexamethasone combination regimen.

The decision tree was the choice for our model as it is usually known to be appropriate for relatively simple models or decision problems "when the outcome set is small and defined and a short time horizon."[17,18] Outcomes or consequences in the decision tree included symptoms, progression, quality-adjusted survival, death, and costs. In medical decision-making, there are many situations where decisions must be made effectively and reliably even though adequate evidence-based data were unavailable for a specific country or target population for the time frame of the desired interest. As defined in the ISPOR-SMDM Modeling Good Research Practices Task Force, decision trees "are a reliable and effective decision-making technique that provides high classification accuracy with a simple representation of currently available research."[18]

Effectiveness data

In the decision tree for the Macedonian health care perspective, because of the absence of country-specific data on disease progression and treatment effectiveness of the MM patients during the last years, the effectiveness data were obtained from the published reports of the randomized clinical trials (GIMEMA M-B02005 and IFM 2005-01) and are summarized in Table 1.[3,19] Husereau et al[19] compared the efficacy of the combination of bortezomib plus dexamethasone with vincristine plus doxorubicin plus dexamethasone, as the induction treatment sequence before ASCT in previously untreated MM patients for a median follow-up of 32.2 months with data collected from medical centers in France and Belgium (for the period 2005–2008). In Cavo et al's study,[3] the compared treatment combinations were TD alone with bortezomib in addition to TD as induction therapeutic sequences before and as consolidation after double ASCT in newly diagnosed MM patients. The study was conducted in several medical centers in Italy for the period 2006–2008.

Table 1 Base-case input effectiveness parameters extracted from randomized clinical trials[3,18]

Input variable	*P*-value	Reference
Complete response after VAD	0.03	19
Complete response after VAD and 1st SCT	0.10	19
Complete response after TD	0.06	3
Complete response after TD and 1st SCT	0.23	3
Complete response after BorD	0.08	19
Complete response after BorD and 1st SCT	0.21	19

Abbreviations: VAD, vincristine, adriamycin, dexamethasone; SCT, stem cell transplantation; TD, thalidomide, dexamethasone; BorD, bortezomib, dexamethasone.

The available effectiveness data in the decision model were mostly reported as rates for different periods.[3,20] All of the rates were converted in the time period of interest (1-, 10-, and 20-year time horizon).[21] In the model, the patients entering the relevant treatment sequence were assumed to have comparable baseline characteristics to participants of the randomized clinical trials used in extracting effectiveness parameters for the model.

Cost analysis

The dosages for each regimen were based on the above-mentioned clinical trials (identified as data sources for the effectiveness data) and the Stojanoski et al study (used to develop the framework of the decision tree model).[3,13,20] The unit costs included were one-time costs that included: per-protocol drug costs, hospital care costs, and ASCT costs (as well as tandem transplantations). Unit costs were obtained from the Central Drug Registry, Agency for Drugs in the Health Ministry in Macedonia during December 2016 as indicated in Table 2.[22]

For VAD, costs were calculated for 4-week cycles (every 28 days) of vincristine 0.4 mg/day and doxorubicin 9 mg/m^2/day, with continuous infusion on days 1–4 plus dexamethasone 40 mg orally on days 1–4 (all cycles) and on days 9–12 and days 17–20 (cycles 1 and 2). Because VAD is an oral regimen, no hospital care costs were necessary.[13,20]

The thalidomide combination strategy with dexamethasone was calculated for 3-week cycles (21 days) with 100 mg thalidomide daily for the first 14 days and 200 mg thalidomide daily, thereafter 40 mg dexamethasone on days 1–4 and 9–12.[3] Furthermore, the bortezomib strategy costs were calculated in four 3-week cycles of bortezomib 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 plus dexamethasone 40 mg on days 1–4 (all cycles) and on days 9–12 (cycles 1 and 2).[20] Additionally, hospital care costs are added for the ASCT first administration and tandem transplantation, respectively. Treatment was continued until the disease progressed and assumed to finish with the further-line treatment and the second ASCT.

Time horizon

To extrapolate the nature of the disease as well as the effectiveness and costs of one-time treatment for a longer period, the impact of 1-, 10-, and 20-year time horizons in the cost-effectiveness results was evaluated. This decision was based on the literature review published before that evaluated the most recent decision-analytic models in MM.[23] In the 1-year model, it is assumed that none of the patients die; however, that is not the case in the 10- and 20-year models, as based on the nature of the disease and the overall survival it should be taken into consideration that a patient could die during that period.

In decision-analytic modeling, studies evaluating costs of a period longer than 1 year, such as those that follow patients from treatment initiation to death, recommend discounting future costs and outcomes.[17,18,24,25] Discounting is how the effects of time are accounted for in economic evaluation. In our study, both cost and health outcomes were discounted at a 3% rate for the 10- and 20-year models (Table 2).

Quality of life data

The outcomes were expressed in units of health utility values derived from the published studies identified from a hand search and the studies identified via the Tuft's Cost-Effectiveness Analysis Registry (Table 3).[22,26–28] The health-related quality of life in those studies was obtained using the EuroQol EQ-5D. The utilities used, as indicated in Table 3, ranged from 0.63 to 0.81 (including induction therapy before and after ASCT) at 6, 12, 18, or 24 months of follow-up.[22,26–28] Utility data were multiplied by years of life for the appropriate model to calculate quality-adjusted life years (QALYs). As we did not identify published data on utility loss due to adverse events for our target population of interest, in the

Table 2 One-time costs derived from the Central Drug Registry, Agency for Drugs in the Health Ministry in Macedonia[27]

Input variable (costs[a])	One-time costs	Costs with 3% discount for 10 years	Costs with 3% discount for 20 years
Costs for VAD	303	225	167
Costs for VAD and 1st SCT	8,806	6,552	4,876
Costs for VAD and 2nd SCT	17,310	12,880	9,584
Costs for VAD and TD	511	380	283
Costs for TD	329	245	182
Costs for TD and 1st SCT	8,833	6,573	4,891
Costs for TD and 2nd SCT	17,337	12,900	9,599
Costs for TD and BorD	5,865	4,364	3,247
Costs for BorD	5,656	4,209	3,132
Costs for BorD and 1st SCT	14,160	10,536	7,840
Costs for BorD and 2nd SCT	22,663	16,864	12,548
Costs for BorD and further lines[b]	11,389	8,474	6,306

Notes: [a]All costs reported in EUR (EUR 1=MKD 61.15), for December 2016. [b]Further-line treatment calculated here is the combination of bortezomib, thalidomide, and dexamethasone.[7]

Abbreviations: VAD, vincristine, adriamycin, dexamethasone; SCT, stem cell transplantation; TD, thalidomide, dexamethasone; BorD, bortezomib, dexamethasone.

Table 3 Base-case utility parameters extracted from published literature via the Tuft's Cost-Effectiveness Analysis Registry[21,25,26]

Input variable	Utility value	Follow-up period	Reference
Complete response after VAD	0.8	12 months	26
Complete response after VAD and 1st SCT	0.62	12 months	26
Complete response after TD	0.81	Prior to relapse	25
Complete response after TD and 1st SCT	0.76	50 months	21
Complete response after BorD	0.81	Prior to relapse	25
Complete response after BorD and 1st SCT	0.645	After relapse	25

Abbreviations: VAD, vincristine, adriamycin, dexamethasone; SCT, stem cell transplantation; TD, thalidomide, dexamethasone; BorD, bortezomib, dexamethasone.

analyses we assumed that there was no difference between treatment combinations in health state utility values related to adverse events of the drugs used.

Cost-effectiveness analysis

Additionally, a CEA of all treatment sequences (VAD vs. TD vs. BorD) prior to ASCT to predict the health effects and costs of each compared alternative was performed. When conducting a CEA study, we calculated the difference between the mean costs of the new intervention and the old one, and this value was divided by the difference of the mean effectiveness (eg, new effectiveness rate minus the old effectiveness rate) to get an incremental cost-effectiveness ratio (ICER). This ratio indicated the needed additional cost to obtain an additional unit of outcome (eg, 1 additional year of life or 1 additional QALY) for the alternative that is shown to be cost-effective.

The ICER was derived as a ratio of the change in costs to incremental benefits of VAD vs. TD vs. BorD (all strategies followed by 1st and 2nd ASCT). The software used for the analysis was TreeAge Pro Healthcare. For the treatment strategies compared, as an outcome, the ICER expressed as cost/QALY gained for each treatment option for 1-, 10-, and 20-year models was calculated.

To allow readers outside of Macedonia to better understand the results of the CEA performed, the costs and ICER values in this paper are reported in Euros. The conversion from Macedonian Denars to Euros was based on the publicly available average Euro–Macedonian Denar exchange rate in December 2016 (EUR 1=MKD 61.15).

Sensitivity analysis

Tornado analysis with a range of ±25% was performed on all values for effectiveness and costs, to determine model stability for the parameter estimation and to highlight which of the variables in the decision analysis could possibly have a significant impact on final cost-effectiveness results. Additionally, the aim of the tornado diagram analysis was to assess the general robustness of the model and key parameters that were identified when conceptualizing and building the model.

Results

The cost calculations were done for the input variables chosen to populate our model. The one-time costs for performing a stem cell transplantation in Macedonia were EUR 8,500 and 1-day hospital daycare costs were around EUR 8 for 1 day. The adjusted one-time costs of the VAD combination therapy were EUR 303 (only VAD) and around EUR 8,800 and EUR 17,310 for the ASCT administered once and the tandem transplantation, respectively. The one-time costs of the TD treatment sequence were higher than VAD for a relatively small difference (EUR 329). However, the one-time costs of the bortezomib treatment sequence were evidently higher than VAD and TD drug regimens (around EUR 5,600); thus, increasing the overall costs of the treatment sequence with bortezomib combination resulted in higher impact in the ICER results. The identified and calculated one-time drug costs are summarized in Table 2.

The estimations of ICER ratios for the 1-, 10-, and 20-year models are presented in Table 4. The ICER was calculated for all combined treatment strategies and the BorD combination dominated in the 1- and 10-year models (discounted and undiscounted) and 20-year undiscounted model from VAD and TD, as presented later in Figure 2A–D. An explanation for this dominance would be the higher price for one-time costs of bortezomib in Macedonia that were calculated to be around 18 times higher than VAD or TD combination treatment options. Based on the cost-effectiveness scatter plot in Figure 1, it can be observed that in the first year VAD has the lowest costs despite the slightly better effectiveness of the TD combination, resulting in considerably higher costs (around EUR 5,400) and the very small difference in only 0.03 QALYs gained with an ICER of EUR 205,600/QALY (Figure 2A). However, in the 10-year model when comparing VAD vs. TD, the ICER decreased to EUR 53,500/QALY gained without discounting the costs and effectiveness parameters, and to EUR 63,800/QALY in the analysis with the performed discounting of 3%, thus resulting in higher effectiveness results of TD compared with VAD for additional 0.29–0.47 QALYs gained (Figure 2B–C).

During the analysis of the undiscounted 20-year model, remarkably higher QALYs gained with the TD regimen compared to VAD (additional 2.55 QALYs gained) with a calculated ICER of EUR 7,600/QALY gained can be observed. In this analysis, it can be observed additionally that the effectiveness of the bortezomib combination is remarkably higher than the VAD combination, with a gain in QALYs of 1.60 compared with the 1- and 10-year models where BorD dominated (Figure 2D). Additionally, in the discounted 20-year model, the bortezomib combination resulted in higher effectiveness than VAD and TD, indicated in Figure 3. The ICER of BorD compared with TD is EUR 138,750/QALY gained; thus, resulting in higher costs for BorD for only 0.43 QALY incremental effectiveness gained. However, when the BorD and TD with the VAD combination in the 20-year discounted model was compared, the VAD

Table 4 ICER analysis for three different regimens for the 1-, 10-, and 20-year decision tree analysis

Treatment sequences/years	TD vs. VAD	BorD vs. TD	BorD vs. VAD
1 year			
ICER (costs/QALY, EUR)	205,611	TD cost saving	VAD cost saving
Incremental effectiveness	0.03	–0.14	–0.17
Incremental costs	5,436	5,691	11,132
10 years (undiscounted)			
ICER (costs/QALY, EUR)	53,448	TD cost saving	VAD cost saving
Incremental effectiveness	0.47	–1.01	–0.54
Incremental costs	25,033	51,840	76,861
10 years (3% discounted)			
ICER (costs/QALY, EUR)	63,764	TD cost saving	VAD cost saving
Incremental effectiveness	0.29	–0.66	–0.37
Incremental costs	18,627	38,578	57,204
20 years (undiscounted)			
ICER (costs/QALY, EUR)	7,564	TD cost saving	VAD cost saving
Incremental effectiveness	2.55	–0.95	1.6
Incremental costs	19,320	108,129	127,458
20 years (3% discounted)			
ICER (costs/QALY, EUR)	TD cost saving	138,747	BorD cost saving
Incremental effectiveness	–1.2	0.43	–1.63
Incremental costs	3,663,892	59,917	91,710

Notes: All costs reported in EUR (EUR 1=MKD 61.15), for December 2016.
Abbreviations: TD, thalidomide, dexamethasone; VAD, vincristine, adriamycin, dexamethasone; BorD, bortezomib, dexamethasone; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

combination dominated and the BorD and TD both showed cost-saving options for respectively higher gained QALYs.

Overall, the lower ICER per QALYs gained is shown in the undiscounted 20-year model with TD resulting as the most cost-saving combination sequence with a slightly better effectiveness of just 2.55 QALYs gained. When considering longer time horizons, the decision makers should consider discounting health outcomes and costs and thus result in considerable changes in the cost-effectiveness results in the discounted 20-years model, as shown in Figure 1 and Figure 3.

Sensitivity analysis

The one-way deterministic sensitivity analyses using a tornado diagram are shown in Figure 4A–C and they represent the most influential variables on the final cost-effectiveness results. The vertical line cutting through all horizontal bars indicates the outcome point estimate corresponding to base-case ICER values. In the tornado diagram, the longest bar placed on the top is the parameter that shows the widest uncertainty, following the other bars that were ordered in decreasing length.

It can be observed that when performing the sensitivity range of ±25%, the most influential parameters that changed the ICER of the 1-year model were: 1) the probability parameter for complete response after induction therapy with VAD treatment sequence; 2) the costs of nonresponders to VAD that are followed by the 2nd treatment sequence with TD; 3) the costs of VAD followed by ASCT and tandem transplantation; and 4) the probability parameter for a complete response after induction therapy with the VAD treatment sequence followed by ASCT (Figure 4A).

Furthermore, in the 10-year discounted model the costs of VAD with ASCT and tandem transplantation compared with other variables still had the greatest impact on the ICER, followed by the costs of the treatment sequence with VAD prior to only one transplantation (Figure 4B).

In the 20-year discounted model the probability of effectiveness data had a very high influence on ICER results, as well as the one-time costs for the TD combination. Other parameters showed slightly or no impact on the cost-effectiveness results of the analyzed models (Figure 4C).

Discussion

To our knowledge, this analysis is the first to assess the economic impact of different treatment sequence regimens in MM prior to ASCT in the perspective of Macedonian health care. Bortezomib-based and thalidomide-based regimens, earlier in randomized clinical trials, have been shown to improve survival and prevent disease progression over the standard of care with VAD as the induction treatment sequence prior to ASCT. Our analysis suggests that the benefit in terms of QALYs gained is higher within all models

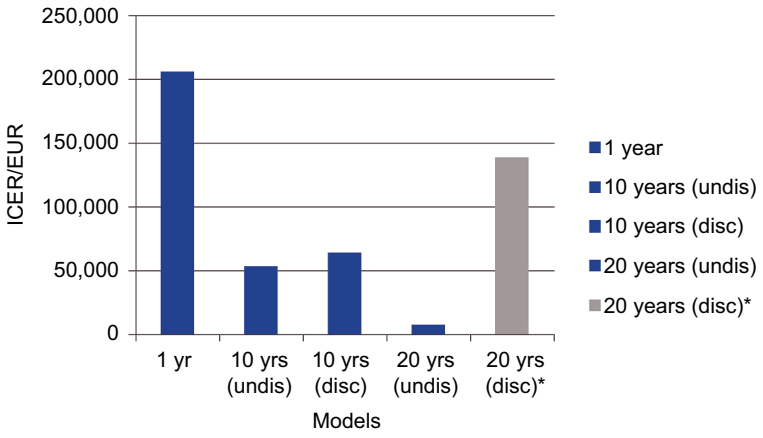

Figure 1 ICER values for the 1-, 10-, and 20-year models. Bortezomib regimen dominated in 1-, 10- (discounted and undiscounted), and 20-year models.
Notes: *Vincristine, adriamycin, and dexamethasone regimen dominated in the discounted 20-year model.
Abbreviations: undis, undiscounted; disc, discounted; ICER, incremental cost-effectiveness ratio; yr, year.

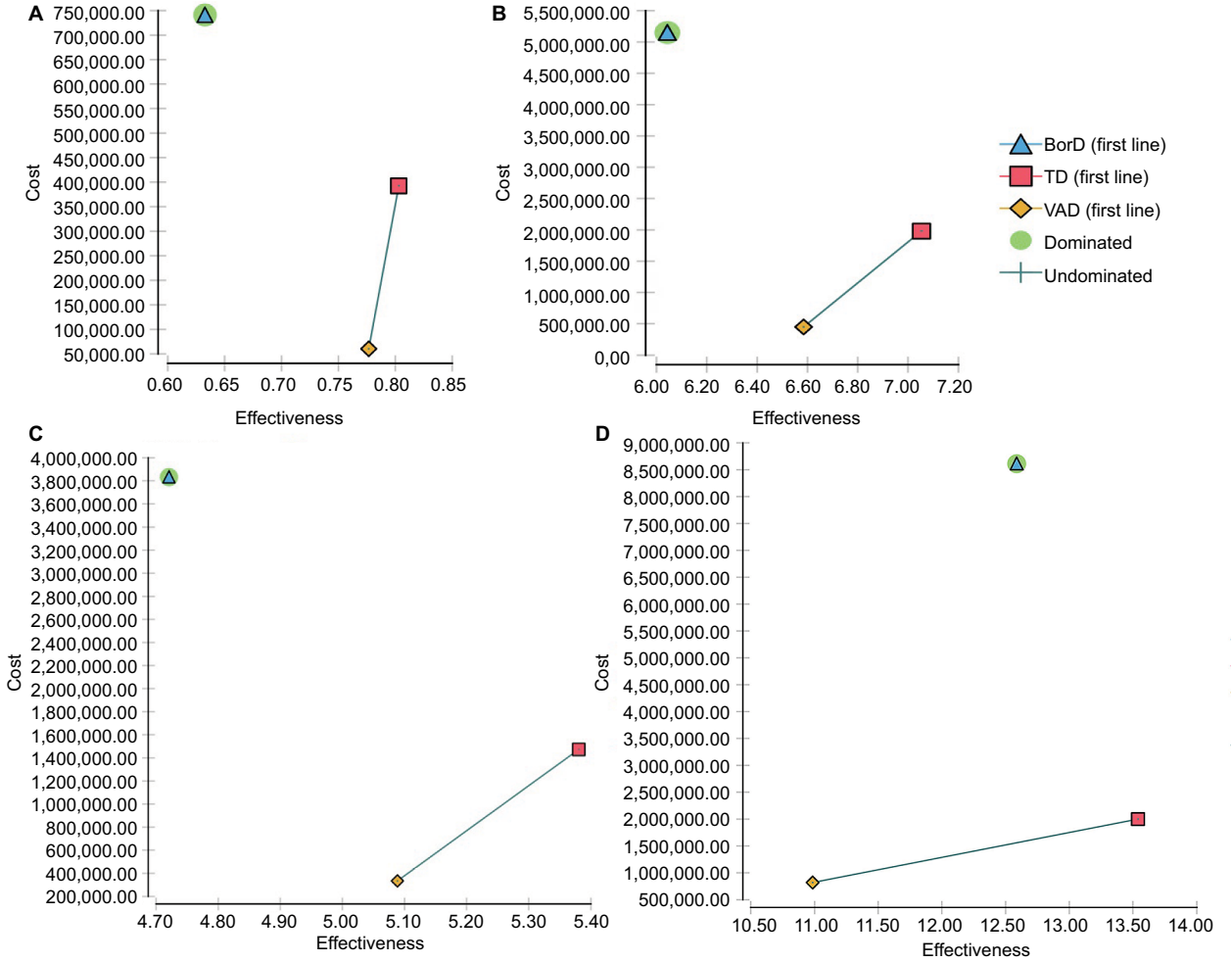

Figure 2 Cost-effectiveness analysis of the 1- and 10-year (discounted and undiscounted) models: (**A**) 1-year model; (**B**) 10-year model, undiscounted; (**C**) 10-year model, discounted by 3%; (**D**) 20-year model, undiscounted.
Notes: Costs in the scatter plot are presented in Macedonian Denars, as the analysis in TreeAge Pro Healthcare was performed in Macedonian Denars.
Abbreviations: Bor, bortezomib; Dex, dexamethasone; TD, thalidomide, dexamethasone; VAD, vincristine, adriamycin, dexamethasone.

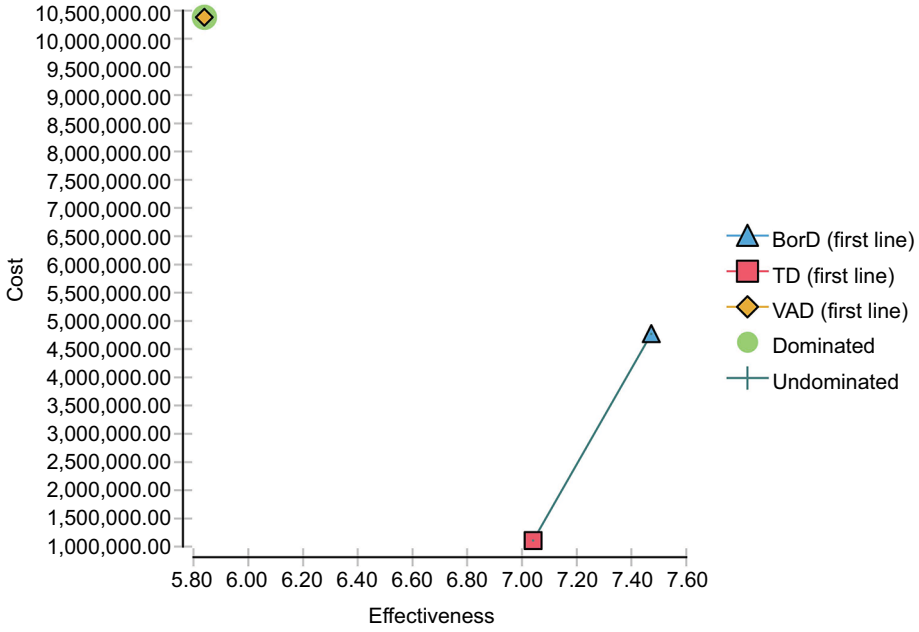

Figure 3 Cost-effectiveness analysis of the 20-year model with 3% discount rate.
Notes: Costs in the scatter plot are presented in Macedonian Denars, as the analysis in TreeAge Pro Healthcare was performed in Macedonian Denars.
Abbreviations: Bor, bortezomib; Dex, dexamethasone; TD, thalidomide, dexamethasone; VAD, vincristine, adriamycin, dexamethasone.

(1, 10, and 20 years) reaching 1.63–2.55 QALYs gained in the 20-year model (discounted and undiscounted), resulting in better survival if we base the choice on the treatment combination that showed as cost-saving and the most effective drug for the respective time horizon.

The aim of this analysis was to provide national Macedonian authorities and health care decision-makers with supportive evidence on the relative effectiveness and incremental cost-effectiveness of the bortezomib-based treatment combination regimen versus thalidomide-based and the standard of care treatments for different scenarios including 1-, 10-, and 20-year time horizons and the discounting of future costs and health outcomes. Additionally, when including the effect of time in the CEA, by using the 3% discount rate, it resulted in different ICER values; thus, highlighting that the decision-makers before deciding on the best treatment strategy should always base their decision on a broader spectrum of evidence including economic evaluations.

To determine whether the new intervention is considered cost-effective, usually, the ICER values should be compared with some selected threshold value that is previously defined by pricing and reimbursement authorities for the specific country where the analysis is done. If the ICER results are lower than the defined threshold value (ie, the incremental cost per outcome of the new intervention is less than the accepted standard), the intervention is considered as cost-effective.[24] The Macedonian pricing and reimbursement authority have not yet defined an explicit cutoff threshold for an ICER value and there is not available an ICER threshold that can be used as a cutoff for our analysis. In order to discuss the results, we could consider the cost-effectiveness threshold used by the World Health Organization and use the alternative threshold value, where the ICER is less than three times the gross domestic product (GDP) per capita for the respective country. The GDP per capita for Macedonia in December 2016 was calculated to be around EUR 5,000. In this context, the cost-effectiveness threshold value for Macedonia would be EUR 15,000 and the strategy that has an ICER that is less than this value will be considered as cost-effective. Based on the results from the analysis from our study, only the results from the undiscounted 20-year model would be considered as the cost-effective strategy; in this case, TD is cost-effective vs. VAD (ICER of EUR 7,600/QALY gained). However, one should be cautious here, as the GDP per capita for Macedonia is very low as it is a low-income country and in development, and it is recommended that policy-makers and decision-makers should explore in more detail before choosing the best willingness-to-pay threshold. If we stick to the World Health Organization criteria, we will face a considerable restriction in the availability of new drugs with better effectiveness and higher costs.

Without taking into consideration the ICER thresholds, in the 1- and 10-year models, as well as the 20-year undiscounted model, it can be observed that TD is the cost-effective

Figure 4 (*Continued*)

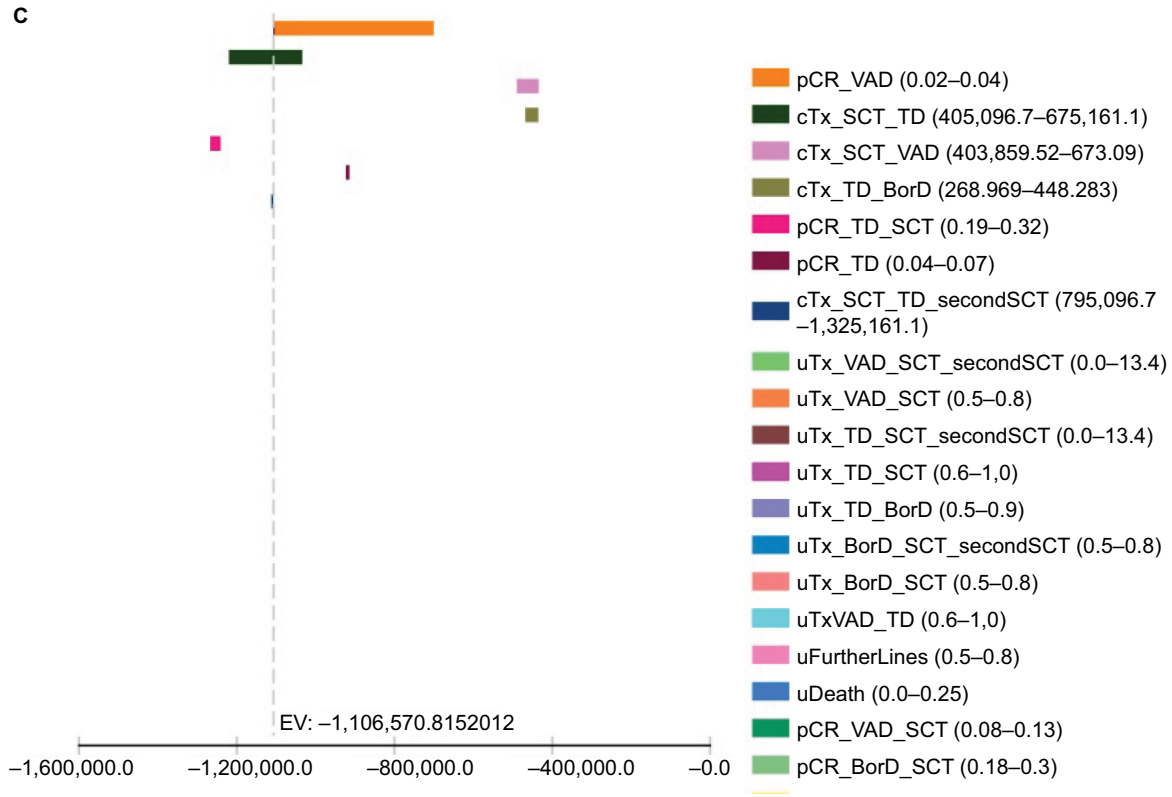

Figure 4 Sensitivity analysis. Tornado diagram with critical variables for the (**A**) 1-year model, (**B**) 10-year model (discounted), and (**C**) 20-year model (discounted). Each bar depicts the overall effect on net benefits as that input is varied across the indicated range of values and their impact on the net monetary benefit. The vertical line indicates the incremental cost-effectiveness ratio. Critical variables are represented as horizontal bars.

Notes: Costs in the scatter plot are presented in Macedonian Denars, as the analysis in TreeAge Pro Healthcare was performed in Macedonian Denar.

Abbreviations: p, probability; CR, complete response; VAD, vincristine, adriamycin, dexamethasone; c, costs; Tx, treatment combinations; TD, thalidomide, dexamethasone; SCT, stem cell transplantation; u, utility; Bor, bortezomib; BorD, bortezomib, dexamethasone.

regimen compared with VAD and cost-saving compared with BorD; however, the landscape changed slightly in the 20-year discounted model with BorD resulting as cost-effective compared with TD and cost-saving with the VAD combination strategy. One response could be the impact that discounting future costs and outcomes has on the decision-analytic modeling and CEA results.

However, in everyday practice, new interventions are not always more costly and more effective compared with the old interventions. The ideal case would be if a new intervention costs less and is more effective; in that case, the new intervention is said to dominate its comparator, meaning that it produces better health outcomes and is less costly. Furthermore, in the 1- and 10-year models the BorD intervention is found to cost more and yet be less effective, resulting in the worst possible case and therefore is not likely to be of interest for the reimbursement authorities. However, this does not have to mean that no further discussion should be enhanced when deciding for the market drug prices of the new interventions that showed better effectiveness results in the randomized clinical trials and better survival beside their current higher costs in the drug market.

In the published literature, there are not so many relevant decision trees that compare treatment strategies as induction treatment before ASCT comparable to the treatment sequences used in Macedonian daily care for MM patients; thus, a cross-study validation of the model was not included in the analysis. Results and conclusions drawn from the decision tree model are based on the information derived from the clinical trials (limited to not available real-world data), and one must be very cautious in interpreting the results and using them in the reimbursement decisions.[17,20,24]

Despite the difficulties involved in integrating information from several clinical trials based on the treatment strategies used in Macedonia for treating MM patients, the model captures the fundamental uncertainties within its analytical framework. The effect of uncertainty and exploring the robustness of our model can be appreciated by considering the effect of decreasing the uncertainty associated with the model parameters that are varied in a range of ±25% value in

the tornado diagram. These results suggest that a substantial amount of uncertainty captured by the model is associated with some of the parameters used for the clinical trials and costs data. In the future, if country-specific data will be available, it is recommended to replicate the model and vary the uncertainty parameters within a probabilistic sensitivity analysis. Furthermore, if a general model will be developed and will include enough comparative strategies to capture the complete MM picture (such as bone symptoms, renal insufficiency, anemia, or hypercalcemia development) throughout the disease progression, further treatment options should be taken into consideration, such as carfilzomib/ixazomib for lytic bone disease; anemia treatment options; etc.

Conclusion

This CEA gives an insight and supports the evidence that the new agent drugs used as induction therapy prior to ASCT for treating MM, such as bortezomib and thalidomide, promise increasing survival and improving quality of life as well as being cost-effective compared to the standard of care therapy for MM patients treated in Macedonia. Given the high mortality rates associated with MM and the age of the affected population, the potential for increasing survival at manageable incremental cost for BorD and TD should be of paramount importance to the decision-makers and reimbursement agencies in Macedonia. Additionally, these results show that providers and payers should put more emphasis on using CEA when deciding the most cost-effective treatment patterns in MM patients for different time horizons and should always consider the effect of time in future costs and health outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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