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LONG-TERM EFFECTIVENESS AND COST EFFECTIVENESS OF MULTIPLE MYELOMA TREATMENT STRATEGIES FOR ELDERLY TRANSPLANT-INELIGIBLE PATIENTS IN SERBIA

DOLGOROČNA USPEŠNOST IN STROŠKOVNA UČINKOVITOST STRATEGIJ ZDRAVLJENJA MULTIPLEGA MIELOMA PRI STAREJŠIH BOLNIKIH, KI NISO PRIMERNI ZA PRESADITEV, V SRBIJI

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ABSTRACT

Introduction: Evidence on long-term effectiveness and cost effectiveness of treatment sequences for multiple myeloma (MM) is sparse. We used published data and country-specific data to assess the cost effectiveness of four-line treatment sequences for elderly transplant-ineligible patients with MM in Serbia.

Method: We developed a Markov cohort model to compare long-term effectiveness and cost effectiveness of five sequential MM treatment alternatives from the perspective of the national healthcare provider. Effectiveness parameters on progression, mortality and adverse events were extracted from published clinical trials. Costs were based on price lists of the National Health Insurance Fund. We compared life expectancy, costs, and incremental cost-effectiveness ratios among alternative courses of action. The model was analyzed over a lifelong time horizon applying a 3% annual discount rate for effectiveness outcomes and costs. Robustness of the model was tested in multiple deterministic sensitivity analyses.

Results: The sequences were defined by the frontline treatment: MPT (melphalan-prednisone-thalidomide), MPV (melphalan-prednisone-bortezomib), CTD (cyclophosphamide-thalidomide-dexamethasone), VCD (bortezomib-cyclophosphamide-dexamethasone) and BP (bendamustine-prednisone). MPV sequence resulted in the highest remaining life expectancy (4.76 life years). Cost-effectiveness analysis resulted in three non-dominated strategies: MPT, VCD, and MPV sequences, with an incremental cost-effectiveness ratio of EUR 35,300 per life-year gained (LYG) for VCD and EUR 47,200/LYG for MPV relative to MPT.

Conclusion: MPV sequence was the most effective in terms of life expectancy for elderly transplant-ineligible MM patients in Serbia. Bortezomib-based strategies would be recommended for the frontline treatment of patients with MM in Serbia if the willingness-to-pay threshold is around EUR 35,000-60,000/LYG.

Keywords: multiple myeloma, sequential treatment, long-term effectiveness, cost effectiveness

IZVLEČEK

Uvod: *O dolgoročni uspešnosti in stroškovni učinkovitosti zaporedij zdravljenja multiplega mieloma (MM) ni veliko dokazov. Na podlagi objavljenih podatkov in podatkov za posamezne države smo ocenili stroškovno učinkovitost štirih zaporedij zdravljenja starejših bolnikov z MM, ki niso primerni za presaditev, v Srbiji.*

Metoda: *Za primerjanje dolgoročne uspešnosti in stroškovne učinkovitosti petih alternativ zaporednega zdravljenja MM z vidika nacionalnega izvajalca zdravstvenega varstva smo razvili kohortni model Markova. Parametre uspešnosti glede napredovanja, umrljivosti in neželenih dogodkov smo pridobili iz objavljenih kliničnih preskušanj. Stroški temeljijo na cenikih nacionalnega sklada za zdravstveno zavarovanje. Med različnimi ukrepi smo primerjali pričakovano življenjsko dobo, stroške in mejno razmerje stroškovne učinkovitosti. Model smo analizirali v vseživljenjskem časovnem okviru, pri čemer smo za rezultate uspešnosti in stroške uporabili 3-odstotno letno diskontno stopnjo. Robustnost modela smo preizkusili z več determinističnimi analizami občutljivosti.*

Rezultati: *Zaporedja so bila opredeljena z zdravljenjem v prvi liniji: MPT (melfalan-prednizon-talidomid), MPV (melfalan-prednizon-bortezomib), CTD (ciklofosfamid-talidomid-deksametazon), VCD (bortezomib-ciklofosfamid-deksametazon) in BP (bendamustin-prednizon). Pri zaporedju MPV je bila pričakovana preostala življenjska doba najdaljša (4,76 leta življenja). Pri analizi stroškovne učinkovitosti so bile ugotovljene tri neprevladujoče strategije: zaporedja MPT, VCD in MPV z mejnim razmerjem stroškovne učinkovitosti 35.300 EUR na pridobljeno leto življenja (LYG) za VCD in 47.200 EUR/LYG za MPV glede na MPT.*

Sklep: *Zaporedje MPV je bilo najuspešnejše v smislu pričakovane življenjske dobe starejših bolnikov z MM, ki niso primerni za presaditev, v Srbiji. Strategije, ki temeljijo na bortezomibu, bi bile priporočljive za zdravljenje bolnikov z MM v prvi liniji v Srbiji, če je prag pripravljenosti na plačilo približno 35.000-60.000 EUR/LYG.*

Ključne besede: *multipli mielom, zaporedno zdravljenje, dolgoročna uspešnost, stroškovna učinkovitost*

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1 INTRODUCTION

Multiple myeloma (MM) is the second most common hemato-oncological disease (1) manifested by an uncontrolled monoclonal malignant proliferation of plasma cells in the bone marrow. MM usually affects elderly people, with a median age of about 65 years at diagnosis (2). The global burden of MM is high and rising, mostly due to the increase in incident cases and mortality of MM in middle-income countries (3). In Serbia, MM is a relatively rare disease occurring in around 200 patients per year (4). The disease prognosis has been changed after the introduction of novel treatment agents, such as thalidomide, bortezomib, and lenalidomide. The improved efficacy of these drugs, in terms of progression-free survival (PFS) and overall survival (OS), was presented in several clinical trials (5-7). However, the novel treatment options are also more costly than the standard melphalan-prednisone treatment (8) and the availability and affordability of these medicines is limited in middle-income European economies (9). In Serbia, thalidomide and bortezomib are used in routine clinical practice. Lenalidomide is recommended as an option for relapsed or resistant disease and has been recently approved (3), but it is still not available in treatment centers across the country and is therefore rarely used. In the current situation of economic crisis that Serbia is going through, the healthcare budget resources directed to the treatment of uncommon diseases are limited and require careful weighing of benefits, harms, and costs of treatment alternatives (10). The novel treatment agents are tested in treatment-naive, relapsed, as well as refractory and heavily pretreated patients. However, evidence about the effectiveness of different sequential treatment combinations is sparse and not easily obtainable in prospective clinical studies, as this would require a large study population and a very long follow up. In addition, healthcare policy decision-making and resource allocation have to be based on a systematic and transparent assessment of benefits, harms, and costs, best addressed by the use of decision-analytic modeling combining different sources of evidence (11).

The aim of this study was to assess the clinical effectiveness and cost effectiveness of common sequential treatment pathways for elderly transplant-ineligible patients with MM in Serbia. Furthermore, our goal was to evaluate whether wider use of lenalidomide in everyday clinical practice would change the model-based recommendations.

2 METHODS

2.1 Model Structure

We adopted the structure of a state-transition Markov model previously developed for the Austrian context (12). To depict treatment patterns in the Serbian healthcare system, important structural changes and parameter adaptations were implemented. To transfer and adapt evidence from another healthcare system to the Serbian national context, we followed a stepwise framework developed for HTA agencies (13). We analyzed the Serbian model over a lifelong time horizon following the established recommendations (14, 15) and a national cost-effectiveness guideline (16). The target population consisted of patients with MM ineligible for stem cell transplantation who were 65 years or older. The model was analyzed from the perspective of the Serbian national healthcare provider. We assessed life expectancy (in life years, LYs), costs (in euros, EUR) and the incremental cost-effectiveness ratio (ICER; in euros per life year gained (LYG)). In the base-case analysis, we applied a 3% annual discount rate for both clinical outcomes and costs (17). The model was programmed in the software TreeAge 2016 (TreeAge Software, Inc. Williamstown, MA).

2.2 Compared Sequential Treatment Strategies

We compared five sequential treatment pathways commonly used for elderly patients with MM in the Serbian healthcare setting. The treatment pathways were based on the national guideline for the treatment of MM (18), adapted by Serbian clinical experts. As front-line treatment options, we assessed combinations of melphalan, prednisone, and thalidomide (MPT); melphalan, prednisone, and bortezomib (MPV); cyclophosphamide, thalidomide, and dexamethasone (CTD); bortezomib, cyclophosphamide, and dexamethasone (VCD); and bendamustine and prednisone (BP). After progression, patients were switched to the second-line treatment with a different mechanism of action (for example, patients on the first-line thalidomide-based protocols were switched to the bortezomib- or lenalidomide-based regimens in the second line) (Table 1).

Table 1. Evaluated treatment sequences.

Treatment sequences			
First-line Tx; Data source	**Second-line Tx; Probability of switching protocol; Data source**	**Third-line Tx Probability of switching protocol; Data source**	**Palliative Tx; Data source**
MPT (19)	1. VCD, 20% of cases (20) 2. VD, 70% (21) 3. RD, 10% (22)	1. RD, 30% (22) 2. BTP, 40% (23) 3. Chemo, 30% *	CP (24, 25)
MPV (26)	1. CTD, 90% (27) 2. RD, 10% (22)	1. RD, 30% (22) 2. BTP, 40% (23) 3. Chemo, 30% *	CP (24, 25)
CTD (28)	1. MPV, 30% (29) 2. VD, 60% (21) 3. RD, 10% (22)	1. RD, 30% (22) 2. BTP, 40% 3. Chemo, 30%*	CP (24, 25)
VCD (30)	1. MPT (31) 2. RD, 10% (22)	1. RD, 30% (22) 2. BTP, 40% (23) 3. Chemo, 30% *	CP (24, 25)
BP (32)	1. RD, 100% (22)	1. BTP, 50% (23) 2. Chemo, 50% *	CP (24, 25)

Legend: B-bendamustine; C-cyclophosphamide; Chemo-standard chemotherapy; D-dexamethasone; M-melphalan; P-prednisone; R-lenalidomide; T-thalidomide; Tx-treatment; V-bortezomib; *, Chemotherapy included the following protocols: DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) (33, 34), DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) (35, 36). Patients switched from first-line treatment to different second- and third-line treatment options. The proportion of patients that switched to each particular protocol is presented in Table 1 (%). Data sources are referenced in parentheses.

As a third-line treatment, patients received a combination of bendamustine, thalidomide, and prednisone (BTP), lenalidomide and dexamethasone (RD) or standard chemotherapy. Palliative treatment consisted of oral administration of low-dose cyclophosphamide and dexamethasone. We assumed administration of a maintenance treatment consisting of daily thalidomide after completion of each treatment protocol, except for RD, which is maintained until progression, and BP recommended for patients with peripheral neuropathy that could deteriorate through thalidomide maintenance.

Figure 1 shows the Markov model with health states and respective state-to-state transitions.

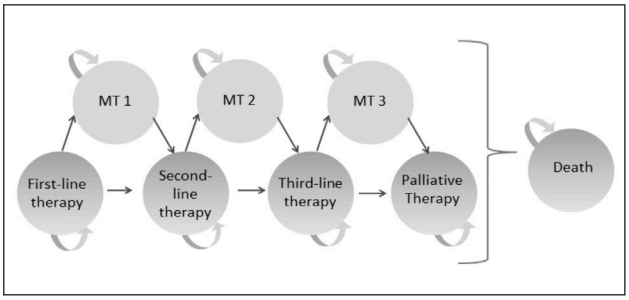

Figure 1. Markov health states and state-to-state transitions. Legend: MT, maintenance treatment; Numbers 1, 2, and 3 indicate the treatment line.

After being diagnosed with MM, all patients received first-line treatment. In the case of relapse or recurrence, patients switched to second-line treatment. If the disease did not progress during the treatment, patients transitioned to the maintenance treatment. Patients could die from MM in the second-line and all subsequent treatmnts, while death from other causes was possible in all the states.

2.3 Natural History and Effectiveness Parameters

The analyzed cohort consisted of 65-year old transplant-ineligible patients with MM. Based on clinical expert estimates, 60% of the population were males. The mortality from causes other than MM was derived from the age- and sex-specific mortality rates reported in the Serbian statistical life tables (37). Guideline-recommended treatment patterns (18) were discussed with nine clinical experts from Serbia within a Delphi panel and revised based on the real-world clinical practice in terms of exact frequency, dose, and route of drug administration. Efficacy data (PFS and OS) and safety data (frequency of grade 3 and 4 adverse events occurring in more than 5% of the study population) were extracted from randomized clinical trials. To derive the first-line treatment effectiveness, we fitted a Weibull curve to the weighted proportions of patients who survived without

progression, extracted from all randomized controlled trials comparing MPT with MP (38). Kaplan Meier curves reported in respective clinical trials (Table 1) were used for the extraction of survival and progression probabilities. Exponential survival models were assumed and excess mortality method was used to derive MM-specific mortality as a difference in overall mortality rates reported in the studies and the mortality from other causes extracted from corresponding life tables. Protocol durations (time to maintenance treatment) were implemented from the guideline recommendations. Probabilities of switching to particular second-line treatment protocols were based on estimates of the Delphi panel (Table 1).

2.4 Costs

A bottom-up micro-costing method was applied to analyze healthcare resource consumption and associated costs (39). Healthcare resource utilization during MM treatment was estimated based on the national guideline (18) and clinical experts' estimates. The unit costs of drug acquisition, diagnostic procedures, hospitalization, outpatient care, and injectable drug administration were extracted from the National Health Insurance Fund (NHIF) databases (40-42) and converted to 2018 euros based on purchasing power parities (1 euro=56.3 Serbian dinars) (43). Details on unit costs and cost calculation can be found elsewhere (39).

2.5 Analyses

In the base-case analysis, we evaluated five sequential four-line MM treatment strategies in terms of remaining life expectancy and cost effectiveness. In order to assess the robustness of the model, we tested the sensitivity of its results to parameter changes. Based on recommendations of the national cost-effectiveness guideline (16), we applied a 1.5% discount rate for clinical outcomes while keeping the 3% discount rate for economic outcomes, and also analyzed the scenario with a 5% discount rate applied to both health outcomes and costs (44).

The incremental cost-effectiveness ratios (ICERs) for the treatment sequences are strongly dependent on the underlying probabilities to switch from the initial treatment to subsequent treatment options. To assess the impact of probabilities of switching to a particular second-line treatment on the model-based recommendations, we structurally adapted the model to assess the cost effectiveness of all potential first- and second-line treatment combinations, analyzing 11 different sequences. The third-line treatment was kept the same.

As lenalidomide is still not available in institutions across Serbia, we varied second- and third-line probabilities of switching to lenalidomide-based protocols from 0 to 'increased by 100%' to account for the possibility of gradually increased administration of lenalidomide in future, once it becomes widely available.

Finally, progression and survival probabilities for third-line chemotherapy were based on observational studies, because of the lack of randomized controlled trials. Therefore, we analyzed the change in the results if we exclude these treatment options from the analysis.

2.6 Model Validation

The face validity of the model was discussed with clinical experts and other decision-analytic modelers. Internal verification of the model was assessed using a thorough examination of parameters, formulas, and codes used in TreeAge by two independent modelers. The health states were mutually exclusive and collectively exhaustive and the rule of symmetrical branching was satisfied (45).

3 RESULTS

3.1 Base-Case Analysis

The base-case analysis resulted in a remaining life expectancy ranging from 3.70 to 4.76 LYs, depending on the treatment sequence (Table 2). The most effective treatment sequence was Starting with MPV with a remaining discounted life expectancy of 4.76 LYs. For comparison, the life expectancy of the general 65-year old population in Serbia is 15.8 years based on the life-table estimates (37).

In the cost-effectiveness analysis, three strategies were identified as non-dominated: Starting with MPT, VCD, and MPV.

Table 2. Discounted base-case analysis results.

Strategy	Cost (€)	Life expectancy (LYs)	ICER (€/LYG)
Starting with MPT	116,500	3.70	-
Starting with CTD	123,400	3.41	Dom
Starting with VCD	126,700	3.99	35,300
Starting with MPV	163,300	4.76	47,200
Starting with BP	373,400	3.98	Dom

Legend: BP, bendamustine, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; Dom, dominated, ICER, incremental cost-effectiveness ratio; LY(s), life year(s); LYG, life year gained; MPT, melphalan, prednisone, thalidomide; MPV, melphalan, prednisone, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; €, euro.

3.2 Scenario and Sensitivity Analyses

The results of the discount rate variations are presented in Table 3. Non-dominated strategies remained the same as in the base-case analysis, but the ICERs changed, as expected.

Table 3. Variation of annual discount rates.

Discount rate →	1.5% for effectiveness; 3% for costs			5% for effectiveness and costs		
Strategy	**Cost (€)**	**Life expectancy (LYs)**	**ICER (€/LYG)**	**Cost (€)**	**Life expectancy (LYs)**	**ICER (€/LYG)**
Starting with MPT	116,500	3.85	-	110,500	3.51	-
Starting with CTD	123,400	3.53	Dom	117,900	3.25	Dom
Starting with VCD	126,700	4.16	32,500	121,800	3.77	43,800
Starting with MPV	163,300	5.01	43,100	156,100	4.47	49,600
Starting with BP	373,400	4.15	Dom	351,800	3.77	Dom

Legend: BP, bendamustine, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; Dom, dominated; Ext Dom, extended dominated; ICER, incremental cost-effectiveness ratio; LY(s), life year(s); LYG, life year gained; MPT, melphalan, prednisone, thalidomide; MPV, melphalan, prednisone, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; €, euro

When we analyzed 11 treatment sequences assuming an equal likelihood of switching to second-line treatment options, four sequences were identified as non-dominated: 1. frontline MPT and VD after treatment failure (MPT→VD), 2. MPT→VCD, 3. MPV→CTD and 4. MPV→RD (Figure 2).

When varying the probability to switch to lenalidomide protocols, non-dominated strategies remained the same (Table 4).

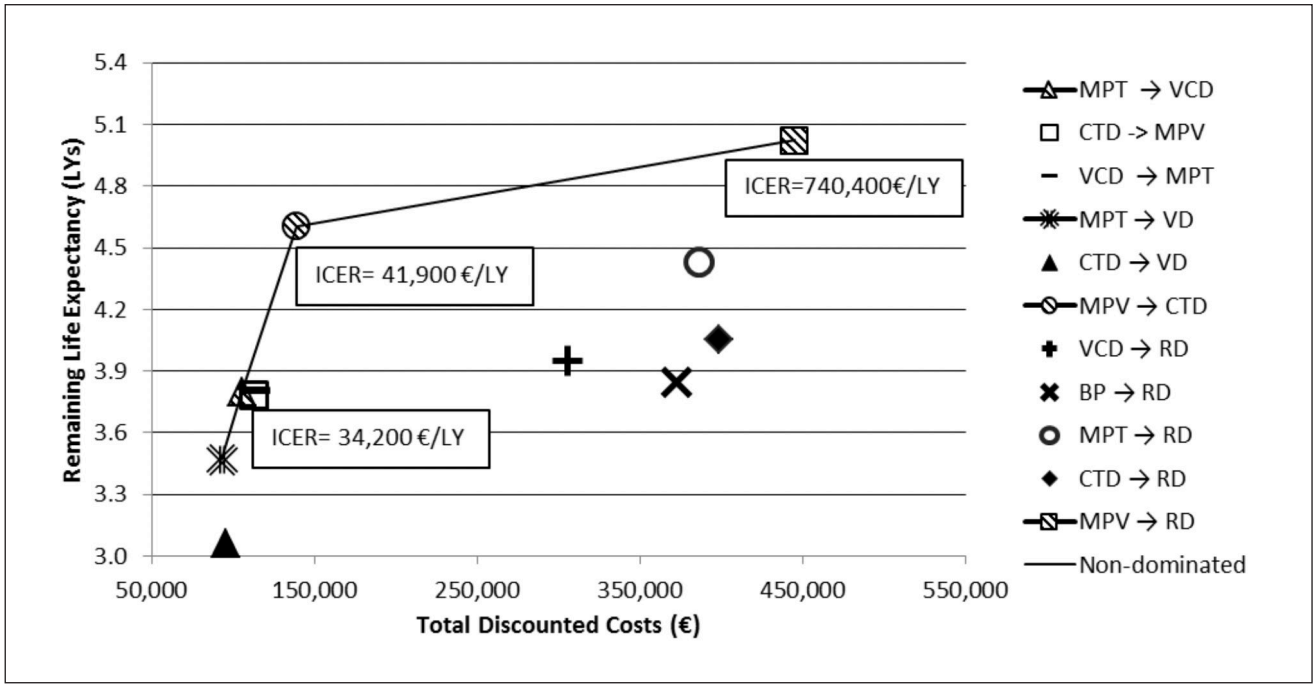

Figure 2. Sensitivity analysis - Cost-effectiveness plane. Sequences defined by the combinations of first- and second-line treatment. The thick line is the cost-effectiveness frontier.

Legend: BP, bendamustine, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; ICER, incremental cost-effectiveness ratio; LY(s), life year(s); MPT, melphalan, prednisone, thalidomide; MPV, melphalan, prednisone, bortezomib; RD, lenalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, dexamethasone; €, euro.

Table 4. Sensitivity analysis results – varying probability of switching to the lenalidomide-based treatment options.

Strategy	Without RD options			Probability of switching to RD increased by 20%			Probability of switching to RD increased by 50%			Probability of switching to RD increased by 100% (i.e., doubled)		
	Cost (€)	Life expectancy (LYs)	ICER (€/LYG)	Cost (€)	Life expectancy (LYs)	ICER (€/LYG)	Cost (€)	Life expectancy (LYs)	ICER (€/LYG)	Cost (€)	Life expectancy (LYs)	ICER (€/LYG)
Starting with MPT	73,000	3.63	-	124,700	3.71	-	137,400	3.73	-	160,300	3.77	-
Starting with CTD	76,900	3.29	Dom	132,800	3.43	Dom	147,300	3.47	Dom	174,200	3.54	Dom
Starting with VCD	82,800	3.89	36,900	136,400	4.00	39,800	151,400	4.03	46,500	178,800	4.09	Ext Dom
Starting with MPV	112,900	4.68	38,000	174,100	4.77	48,700	190,600	4.80	51,000	220,200	4.84	55,800
Starting with BP*	373,400	3.98	Dom	373,400	3.98	Dom	373,400	3.98	Dom	373,400	3.98	Dom

Legend: BP, bendamustine, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; Dom, dominated; ICER, incremental cost-effectiveness ratio; LY(s), life year(s); LYG, life year gained; MPT, melphalan, prednisone, thalidomide; MPV, melphalan, prednisone, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; €, euro
*BP had a 100% probability of switching to lenalidomide-based treatment in the base-case analysis; thus the results remained the same.

An additional analysis was performed to assess robustness of the results if we assume no use of chemotherapy as a third-line treatment option. In this case, life expectancies and costs of the strategies were notably higher (Table 5). The strategies remaining non-dominated were the MPT sequence and the MPV sequence with an ICER of EUR 55,800/LY.

Table 5. Sensitivity analysis – ranking of the sequences when excluding the third-line chemotherapy.

Strategy	Cost (€)	Life expectancy (LYs)	ICER (€/LYG)
Starting with MPT	210,200	4.40	-
Starting with CTD	223,100	4.16	Dom
Starting with VCD	251,100	4.92	Ext Dom
Starting with MPV	266,000	5.53	55,800
Starting with BP	390,200	4.92	Dom

Legend: BP, bendamustine, prednisone; CTD, cyclophosphamide, thalidomide, dexamethasone; Dom, dominated; Ext Dom, extended dominated; ICER, incremental cost-effectiveness ratio; LY(s), life year(s); MPT, melphalan, prednisone, thalidomide; MPV, melphalan, prednisone, bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; €, euro.

4 DISCUSSION

Based on the results of our analysis, the sequence with frontline MPV provides the most beneficial outcome in terms of life expectancy. The treatment sequences starting with bortezomib-based protocols were cost effective for the treatment of transplant-ineligible elderly patients with MM in Serbia compared to thalidomide- and bendamustine-based protocols, if the willingness-to-pay (WTP) threshold is around EUR 35,000-60,000/LYG. A more detailed assessment of the compared strategies, taking into account first- and second-line treatment combinations, resulted in four non-dominated strategies: MPT→VD, MPT→VCD, MPV→CTD, MPV→RD. Our analysis shows that, if the NHIF is willing to pay around EUR 40,000/LYG, the options starting with MPV should be favored in the treatment of elderly patients with MM. Keeping in mind that the annual gross domestic product per capita (GDP) in Serbia in 2017 (the last reference year) was EUR 10,700, the implementation of the MPV→CTD sequence might be considered cost effective from the country's perspective (43). The World Health Organization considers an intervention cost effective if its cost per disability-adjusted life-year averted (DALY) is less than three times a country's annual GDP per capita (46). We were unable to calculate DALYs due to the lack of country-specific and detailed disease-specific disability weights. However, we can assume that the MPV→RD sequence, with an ICER of over EUR 700,000/LYG, would not be considered cost effective in Serbia.

A systematic literature review that assessed the cost effectiveness of bortezomib-based options for treatment of MM, reported that the bortezomib-based regimens were cost effective in most of the published reports (47).

However, the cost-effectiveness reports assessed the health-economic impact of bortezomib-based regimens considering only one treatment line, as a first-line treatment or after relapse (47). Only one study analyzed the lifelong sequential MM treatment. Based on this study, the sequence potentially providing better survival outcomes in a group of elderly patients in the Dutch setting was thalidomide → lenalidomide → bortezomib (48).

The decision-analytic model that evaluated the cost utility of different first-line MM treatments in transplant-ineligible patients from the US perspective identified the MPV treatment as cost saving in comparison to MPT and melphalan, prednisone and lenalidomide with lenalidomide maintenance (49). However, it must be noted that thalidomide is available only at a patent-protected price in the US, while in Serbia a generic drug is available at a much lower price than bortezomib (EUR 12 vs. EUR 655 per unit).

Like all decision-analytic modeling studies, our study has several limitations, since the model development required several assumptions to be made. The model was constructed based on the Serbian national guideline recommendations and Serbian clinical experts' opinions. However, the results of the Delphi panel implied that different treatment pathways might be used across different institutions and among clinical experts in Serbia. Thus the results of our analysis might not be exhaustive enough to cover all treatment-related issues in daily clinical routine. Therefore, it would be important to confirm our findings by parameterizing the model with real-world effectiveness data. Furthermore, we systematically searched for the studies that match the guideline-recommended treatment patterns used in Serbia. However, the drug dosing and frequency and route of administration were not always perfectly matched. Survival estimates extracted from trials were modified to disease-specific survival estimates, and Serbian life-tables were applied to simulate the life-expectancy of the model population. This challenging task required complex modeling and a number of assumptions; still, it allowed us to adjust the outcomes of international trials to a specific country population. After patients progressed, we assumed the effectiveness of the subsequent treatment to be independent of the type of prior treatments. This might not be the case in the real world, since drugs with a common mechanism of action may also have similar resistance pathways. However, the patients in our analysis were assigned to a treatment utilizing a different mechanism of action after failure, except for the sequence assuming switching from thalidomide-based protocols to lenalidomide, which was found to be unaffected by previous thalidomide therapy (50). Finally, our model did not consider the quality of life of patients on different treatments, because the evidence was sparse and the implementation of existing data would diminish the robustness of our results. Further research should address the gap in treatment-specific utility estimates, which will provide a solid basis for cost-utility analysis.

The comparison of benefits, harms, and costs of relevant alternatives is stressed as a necessity for healthcare policy decision making in the European Union (51) as well as in Serbia (52, 53). Our analysis provides an insight into a daily clinical routine and commonly used treatment pathways and synthesizes the data from different sources in order to assess the clinical and economic impact of lifelong MM treatment in Serbia.

5 CONCLUSION

In conclusion, sequential MM treatment with frontline MPV achieves the highest remaining life expectancy for the elderly transplant-ineligible population. This treatment sequence can be considered cost-effective from the Serbian health care perspective if the WTP threshold ranges from EUR 35,000-60,000/LYG.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

Ethical approval was not required as patients were not included in the study.

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