COSTS OF SEQUENTIAL MULTIPLE MYELOMA TREATMENT FOR ELDERLY TRANSPLANT-INELIGIBLE PATIENTS IN THE SERBIAN HEALTH CARE SYSTEM

Introduction. Multiple myeloma is an incurable plasma-cell proliferation mainly affecting the elderly population. The aim of this study was to analyze treatment patterns, utilization of health resources and treatment costs of multiple myeloma in the elderly patients ineligible for autologous hematopoietic stem cell transplantation in Serbia. Material and Methods. The analysis of the healthcare costs, from the perspective of the Serbian healthcare system, took into account the costs of medications, diagnostic procedures, inpatient and outpatient care, as well as the costs of drug administration and management of drug adverse effects. Results. Thalidomide based regimens were less costly than bortezomib-based regimens (average per-protocol costs 6,000 € vs. 64,700 €, respectively). The most expensive treatment regimen was lenalidomide-deksametazon (average per-protocol costs 145,200 €). The sequential (four-line therapy) treatment costs varied from 85,800 €, starting with melphalan-prednisone-thalidomide to 153,800 €, starting with melphalan-prednisone-bortezomib treatment protocol. The estimated costs did not significantly differ during variation of the parameters in the sensitivity analysis. Conclusion. The costs of multiple myeloma treatment in the Republic of Serbia are mainly driven by the cost of anti-myeloma drugs. The most expensive treatment sequence was starting with melphalan-prednisone-bortezomib treatment protocol.

Key words: Multiple Myeloma; Cost-Benefit Analysis; Economics, Pharmaceutical; Clinical Protocols; Aged; Serbia

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Introduction

Multiple myeloma (MM) is an incurable malignant plasma-cell proliferation manifesting with bone pain, hypercalcemia, anemia, renal insufficiency and malaise [1]. It accounts for approximately 10% of all hematologic malignancies worldwide and it commonly affects the elderly population, and the median age at diagnosis is between 65 and 70 years [2]. The incidence of hematologic malignancies is remarkably lower in Eastern European coun-
tries, although it is not completely clear whether the reason is a genuinely small number of cases, under-diagnosis or under-reporting [3]. In 2014, 184 newly diagnosed cases were identified in Central Serbia [4]. The disease outcomes, expressed in terms of overall survival and progression-free survival (PFS), have been significantly improved after the introduction of novel immunomodulatory and proteasome inhibitor-based therapies [5]. The standard melphalan-prednisone treatment regimen for elderly transplant-ineligible MM patients has been ameliorated by incorporating the potent novel agents – thalidomide, bortezomib, and lenalidomide. Novel two- and three-drug combinations have been recommended for elderly transplant-ineligible MM patients in the United States of America (USA) [6], Europe [2, 7], as well as in Serbia [8] after assessing their effectiveness in clinical trials. However, the favorable health outcomes are associated with significantly higher costs, emphasizing the need for a pharmaco-economic evaluation. Only a third of cancer indications approved for treatment with targeted cancer therapies by the European Medicines Agency are reimbursed in Serbia [9]. There is a lack of published data on the reimbursement decisions and availability of novel MM treatment options in the Serbian setting. A previously published systematic literature review showed that there were no studies published on economic aspects of MM outside of the USA and Western Europe [10]. Due to constraints on the healthcare budget and an economic crisis spanning the last few decades, an assessment of the costs of alternative treatments in the Serbian setting is essential for a rational allocation of resources. The need for adopt-
ing pharmaco-economic aspects in healthcare policy decision making in Serbia is emphasized in case of MM, as a rare life-long treated disease with a spectrum of different medications some of which are available only at high costs. The economic burden of the MM is expected to steadily rise along with the aging of the Serbian population and also with prolonged patient survival due to novel drug generations. The aim of our study was to ascertain the treatment patterns available for elderly non-transplant eligible MM patients in Serbia, to analyze the total costs of different sequential treatment lines, and to guide efficient resource allocation by providing an insight into the costs of MM-related healthcare services.

**Material and Methods**

We have performed a micro-costing study from the perspective of the national health system of the Republic of Serbia. An Excel-based cost estimator was developed with the goal of assessing the total direct costs of sequential treatment options commonly used in the Serbian healthcare setting for elderly non-transplant eligible MM patients. Treatment options for the selected subgroup of patients were defined following the guidelines for diagnosis and treatment of MM in Serbia [8] and a clinical expert’s opinion (coauthor A. Savić). In order to assess the lifetime per-patient costs, we considered three sequential treatment lines followed by palliative treatment (Table 1). The principles of MM management in our analysis are based on the Serbian national clinical guidelines [8]. Further details, such as the frequency of diagnostic procedures throughout the treatment, duration of hospitalization for different treatment protocols, the necessity of physician examinations etc., were provided by nine clinical experts from Serbia in a three-round Delphi panel. The Delphi panel is a well-established method to achieve a consensus on clinical experts’ opinion on a topic in their field of interest [11]. An overview of the drug protocols currently used in the Serbian clinical setting is presented in Table 2 [12–29]. We assessed the costs of five different first-line treatment options and possible sequential treat-

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**Table 1. Assessed treatment sequences**

| Analyzed Treatment Sequences/Analizirane terapijske sekvence |
|-------------------------------------------------------------|
| First-line Tx/Prva linija Tx | Second-line Tx/Druga linija Tx | Third-line Tx/Treća linija Tx | Palliative Tx/Palijativna Tx |
| MPT → VCD/VD/RD → RD/BTP/Chemo → CP |
| MPV → CTD/MPT/RD → RD/BTP/Chemo → CP |
| CTD → MPV/VD/RD → RD/BTP/Chemo → CP |
| VCD → MPT/ RD → RD/BTP/Chemo → CP |
| BP → RD → BTP/Chemo → CP |

**Legend/Legenda:** B - bendamustine; C - cyclophosphamide; Chemo-standard chemotherapy/standardna hemioterapija; D - dexamethasone; M - melphalan; P - prednisone; R - lenalidomide; T - thalidomide; Tx - treatment/terapija; V - bortezomib
**Table 2.** Treatment protocols used in the clinical practice  
**Tabela 2.** Terapijski protokoli koji se primenjuju u kliničkoj praksi

| Protocol description | Recommended treatment duration and median treatment duration (MTD) reported in the trials Preporučeno trajanje tretmana i srednje trajanje tretmana (MTD) prijavljeno u studijama | Median progression-free survival (PFS) Srednje vreme preživljavanja bez progresije bolesti (PFS) | Source Izvor |
|----------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------|
| BP, 1st-line/prva linija  
Bendamustine, 120-150 mg/m²/d., i.v., on days/na dan 1, 2  
Prednisone, 60 mg/m²/d., p.o., on days/na dan 1 - 4 | 6 4-week cycles/cetvoronedeljnih ciklusa | MTD: 6.8 m.  
PFS: 14 m. | Ponisch, 2006 [12] |
| CTD, 1st-line/prva linija  
Cyclophosphamide, 500 mg , i.v., on days/na dan 1, 8, 15  
Thalidomide, 100-200 mg/d., p.o.  
Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 and 17 - 20 | 6 4-week cycles/cetvoronedeljnih ciklusa | MTD, 1st line/prva linija : 9 m.  
PFS, 1st line/prva linija: 13 m. | 1st line/prva linija: Morgan, 2011 [13] |
| CTD, 2nd-line/druga linija  
Cyclophosphamide, 500 mg/m², i.v., on day/na dan 1  
Thalidomide 100 mg/d., p.o.  
Dexamethasone 40 mg/d., i.v. on days/na dan 1 - 4 and 4 and 17 - 20 | 6 4-week cycles/cetvoronedeljnih ciklusa | MTD, 2nd line/druga linija : 6 m.  
PFS, 2nd line/druga linija: 10 m. | 2nd line/druga linija: Dnossyanka, 2010 [14] |
| MPT, 1st- & 2nd-line/prva i druga linija  
Melphalan, 4 mg/m²/d., p.o., 7 days/dana  
Prednisone, 40 mg/m²/d., p.o., 7 days/dana  
Thalidomide, 100 mg/d., p.o. | 6 4-week cycles/cetvoronedeljnih ciklusa | MTD 1st line/prva linija: 9.6 m.  
MTD 2nd line/druga linija: 4 m. | 1st line/prva linija: Palumbo, 2008 [15]  
2nd line/druga linija: Palumbo, 2006 [16] |
| MPV, 1st-line/prva linija  
a) Melphalan, 9 mg/m²/d., p.o., on days/na dan 1 - 4  
Prednisone, 60 mg/m²/d., p.o., on days/na dan 1 - 4 | 1st line/prva linija 6 4-week cycles/cetvoronedeljnih ciklusa | PFS, 1st line/prva linija: 24 m. | 1st line/prva linija: San Miguel, 2008 [17] |
|  
b) Bortezomib, 1.3 mg/m², i.v. on days/na dan 1, 4, 8, 11, 22, 25, 29, 32  
Prednisone, 60 mg/m²/d., p.o., on days/na dan 1 - 4 | 5 4-week cycles/cetvoronedeljnih ciklusa | MTD, 1st line/prva linija: 11.5 m | 1st line/prva linija: San Miguel, 2008 [17] |
|  
b) Melphalan, 9 mg/m²/d., p.o., on days/na dan 1 - 4  
Prednisone, 60 mg/m²/d., p.o., on days/na dan 1 - 4 | 2nd line/druga linija 9 4-week cycles/cetvoronedeljnih ciklusa | PFS, 2nd line/druga linija: 18 m. | 2nd line/druga linija: Petrucci, 2013 [18] |
| MPV, 2nd-line/druga linija  
Melphalan, 24 mg/d., p.o., 28 days (dana)  
Prednisone, 50 mg every other day/svakog drugog dana, p.o.  
Bortezomib, 1.3 mg/m², i.v., on days/na dan 1, 8, 15, 22 | MTD, 2nd line/druga linija: ND |  |  |
| Rd, 2nd and 3rd line/druga i treća linija  
Lenalidomide, 25 mg/d., p.o., on days/na dan 1 - 21  
Dexamethasone 40 mg/d., i.v., on days/na dan 1 - 4, 9 - 12, 17 - 20 | 4-week cycles until progression/četvoronedeljni ciklusi do progresije bolesti | MTD 2nd-line/druga linija: 12.5 m.  
PFS 2nd-line/druga linija: 14.1 m. | Stadtmaurer, 2009 [19] |
|  
MTD 3rd-line/treća linija: 9.2 m.  
PFS 3rd-line/treća linija: 9.5 m. |  |  |  |
ment alternatives for a second- and third-line and palliative treatment. The total direct costs for MM management and treatment comprised the expenditures for drugs, diagnostic procedures, inpatient and outpatient care, administration of injectable drugs and management of adverse events for each treatment protocol. The healthcare service activities and the respective cost items are presented in Scheme 1. We followed the recommendations of the guidelines for disease-specific costing studies in low- and middle-income countries [30]. All costs were priced in 2016 and the values were converted to Euros (€)

| VCD, 1st- & 2nd-line/prva i druga linija | 8 3-week cycles/tronedeljnih ciklusa | MTD, 1st line/prva linija: 4.5 m. | PFS, 1st line/prva linija: 21 m. | 1st line/prva linija: Kumar, 2012 [20] |
|----------------------------------------|------------------------------------|----------------------------------|---------------------------------|-------------------------------------|
| Cyclophosphamide, 500 mg i.v. on days/na dan 1, 8, 15 | | | | |
| Bortezomib, 1.3 mg/m², i.v., on days/na dan 1, 4, 8, 11 | | | | |
| Dexamethasone, 20 mg/d., i.v., days/na dan 1, 2, 4, 5, 8, 9, 11, 12 | | | | |

| VD, 2nd-line/druga linija | 8 3-week cycles/tronedeljnih ciklusa | MTD: 3.5 m. | PFS: 7.4 m. | Hjorth, 2012 [22] |
|--------------------------|------------------------------------|-----------------|-----------------|-----------------|
| Bortezomib, 1.3 mg/m², i.v., on days/na dan 1, 4, 8, 11 | | | | |
| Dexamethasone, 20 mg, i.v., on days/na dan 1, 2, 4, 5, 8, 9, 11, 12 | | | | |

| BPT, 3rd-line/treća linija | 6 4-week cycles/četvoronedeljnih ciklusa | MTD: 5.5 m. | PFS: 12 m. | Poenisch, 2008 [23] |
|---------------------------|----------------------------------------|-----------------|-----------------|-----------------|
| Bendamustine, 60 mg/m², i.v., on days/na dan 1, 8, 15 | | | | |
| Prednisone, 100 mg, p.o., on days/na dan 1, 8, 15, 22 | | | | |
| Thalidomide, 100 mg, p.o., on days/na dan 1 - 28 | | | | |

| Chemotherapy, 3rd-line/treća linija | DCEP 6 3-week cycles/tronedeljnih ciklusa | DCEP MTD: 1.5 m. | PFS: 3.7 m. | Park, 2014, obs. [24] |
|------------------------------------|----------------------------------------|-----------------|-----------------|-----------------|
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| DT-PACE 2 6-week cycles/šestonedeljnih ciklusa | | | | |
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Thalidomide, 200 mg, p.o., on days/na dan 1 - 28 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Doxorubicin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days (na dan) 1 - 4 | | | | |

| Chemotherapy, 3rd-line/treća linija | DCEP 6 3-week cycles/tronedeljnih ciklusa | DCEP MTD: 1.5 m. | PFS: 3.7 m. | Park, 2014, obs. [24] |
|------------------------------------|----------------------------------------|-----------------|-----------------|-----------------|
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| DT-PACE 2 6-week cycles/šestonedeljnih ciklusa | | | | |
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Thalidomide, 200 mg, p.o., on days/na dan 1 - 28 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Doxorubicin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days (na dan) 1 - 4 | | | | |

| Chemotherapy, 3rd-line/treća linija | DCEP 6 3-week cycles/tronedeljnih ciklusa | DCEP MTD: 1.5 m. | PFS: 3.7 m. | Park, 2014, obs. [24] |
|------------------------------------|----------------------------------------|-----------------|-----------------|-----------------|
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| DT-PACE 2 6-week cycles/šestonedeljnih ciklusa | | | | |
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Thalidomide, 200 mg, p.o., on days/na dan 1 - 28 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Doxorubicin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days (na dan) 1 - 4 | | | | |

| Chemotherapy, 3rd-line/treća linija | DCEP 6 3-week cycles/tronedeljnih ciklusa | DCEP MTD: 1.5 m. | PFS: 3.7 m. | Park, 2014, obs. [24] |
|------------------------------------|----------------------------------------|-----------------|-----------------|-----------------|
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| DT-PACE 2 6-week cycles/šestonedeljnih ciklusa | | | | |
| Dexamethasone, 40 mg/d., i.v., on days/na dan 1 - 4 | | | | |
| Thalidomide, 200 mg, p.o., on days/na dan 1 - 28 | | | | |
| Cisplatin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Doxorubicin, 10 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Cyclophosphamide, 400 mg/m², i.v., on days/na dan 1 - 4 | | | | |
| Etoposide, 40 mg/m², i.v., on days (na dan) 1 - 4 | | | | |

| CP, palliative treatment/palijativni tretman | Continuous/ Kontinuirano | Median overall survival/srednje vreme preživljavanja: 16.4 m. | PFS: 11.6 m. | Weerdt, 2001, obs. [28] |
|------------------------------------------|------------------------|----------------------------------|-----------------|-----------------|
| Cyclophosphamide, 50 mg/II d., p.o. | | | | |
| Prednisone, 30 mg/II d., p.o. | | | | |

Legend/Legenda: * MTD based on opinion of the clinicians from Serbia (Delphi panel) MTD na osnovu mišljenja srpskih kliničara; B - bendamustine; C - cyclophosphamide; Chemo - chemotherapy/hemioterapija; d - day/dan; D - dexamethasone; i.v. - intravenous administration/intravenska primena; M - melphalan; m. - months/meseći; ND - not determined/nije ustanovljeno; obs. - observational studies/obzervacione studije; P - prednisone; p.o. - oral uptake/oralni unos; R - lenalidomide; T - thalidomide; Tx - treatment/terapija; V - bortezomib
Drug costs, costs of diagnostic procedures, inpatient and outpatient costs were provided by the National Health Insurance Fund (NHIF) of the Republic of Serbia [32]. The complete list of the analyzed drugs, their administration and the sources are shown in Table 2. The unit costs for staff, hospital day and injectable drug application were extracted from the NHIF’s price list for health services for secondary and tertiary medical care [33]. The costs of prophylaxis and adverse events management were based on the frequency of their occurrence extracted from the respective clinical trials. The principles of management of these events are described in the guidelines for the management of adverse events in elderly MM patients [34] and adapted for the clinical setting by Serbian clinical experts. To estimate the total direct costs, we used the bottom-up micro-costing methodology, since it results in the most precise cost estimates for health care [30]. Average patient costs were calculated by multiplying unit costs with the corresponding health resource consumption. We estimated per-protocol costs in each treatment line and the total direct per-patient cost of the life-long MM treatment for the alternative treatment sequences. The sequence costs were calculated based on the protocol costs, the survival probability and probability to switch to a particular subsequent treatment, discounted over the sequence duration. The sequence duration was calculated as a discounted sum of the reported median PFS for each of the treatment protocols in the sequence, taking into account the probability to switch to a particular subsequent treatment. Furthermore, we as-

### Table 3. Sensitivity analysis; Varying the annual discount rate; Total costs and median sequence duration for the treatment strategies

| Treatment Sequence | Base-Case (3% discount rate for costs and effectiveness outcomes) | Recommendations of the Serbian guideline for farmacoeconomic evaluations (3% discount rate for costs and 1.5% for effectiveness outcomes) Preporuke vodiča za farmakoe-konomsko analize u Srbiji (3%-na diskontna stopa na troškove i 1.5%-na diskontna stopa na ishode) | (5% discount rate for costs and effectiveness outcomes) | (5%-na diskontna stopa na troškove i ishode) |
|--------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------|
| Starting with MPT  | analyse referentnog slučaja (3%-na diskontna stopa na troškove i ishode) | Analiza referentnog slučaja (3%-na diskontna stopa na troškove i ishode)                                                                                                                                                                                                                   |                                                   |                                           |
| Sequence Costs (€) | Sequence Duration (months) | Sequence Costs (€) | Sequence Duration (months) | Sequence Costs (€) | Sequence Duration (months) |
| 85,800              | 49.3                  | 85,800             | 50.9                  | 82,100              | 47.3                  |
| 96,400              | 42.8                  | 96,400             | 44.0                  | 93,200              | 41.3                  |
| 153,800             | 51.8                  | 153,800            | 53.5                  | 148,700             | 49.6                  |
| 118,600             | 48.4                  | 118,600            | 49.9                  | 114,800             | 46.4                  |
| 150,200             | 42.4                  | 150,100            | 43.6                  | 145,300             | 40.9                  |

Legend/Legenda: BP – bendamustine-prednisone; CTD - cyclophosphamide, thalidomide, dexamethasone; MPT – melphalan, prednisone, thalidomide; MPV – melphalan, prednisone, bortezomib; VCD – bortezomib, cyclophosphamide, dexamethasone; € - Euro/Evro

### Graph 1. Direct per-protocol costs of the analyzed treatment regimens

**Grafikon 1. Direktni troškovi analiziranih terapijskih protokola**

Legend/Legenda: AE - adverse events/neželjeni efekti; B - bendamustine; C - cyclophosphamide; Chemotheraphy/hemio-terapija; D - dexamethasone; Dg - diagnosis/dijagnostika; M - melphalan; P - prednisone; R - lenalidomide; T - thalidomide; V - bortezomib. The numbers (1, 2, 3) indicate the treatment line/ Brojevi (1, 2, 3) upućuju na liniju terapije
sessed the uncertainty of the cost estimates in several deterministic sensitivity analyses. We varied the discount rate, the protocol duration and the probabilities of switching to the second- and third-generation treatment alternatives.

**Results**

Per-protocol costs varied significantly among the treatment alternatives in all treatment lines (Graph 1). Costs of thalidomide-based protocols in the first (melphalan-prednisone-thalidomide (MPT): 13,100 €, cyclophosphamide-thalidomide-dexamethasone (CTD): 12,500 €) and second line (MPT: 8,000 €, CTD: 10,900 €) were notably lower than the costs of bortezomib-based protocols (first line, melphalan-prednisone-bortezomib (MPV): 98,800 €, bortezomib-cyclophosphamide-dexamethasone (VCD): 65,800 €; second-line, melphalan-prednisone-bortezomib (MPV): 67,500 €, bortezomib-cyclophosphamide-dexamethasone (VCD): 63,400 €, bortezomib-dexamethasone (VD): 59,200 €). The highest per-protocol costs were estimated for lenalidomide-dexamethasone (RD) protocols (second line: 181,200 €, third line: 133,700 €). Per-protocol costs were mainly driven by the drug acquisition costs, although the share of this cost component varied among the protocols (29 – 92%) (Graph 1). The exception was pallia-
is still not available in all the institutions in Serbia. In the sensitivity analysis, we analyzed the robustness of our results if we do not consider lenalidomide-based alternatives as an option in second- and third-line treatment. Furthermore, we analyzed the possibility that lenalidomide-based alternatives will be used more often in the clinical setting once they become available, so we increased the probability of switching to RD from the baseline value of 0.1 to 0.3 in the second-line, and from the baseline value 0.35 to 0.55 in the third-line setting, based on the results of the Delphi panel. The sensitivity analysis showed that incorporation of lenalidomide in the common treatment pathways increased the costs of the alternative sequential treatments by 30% on average, but also prolonged survival (treatment duration) on average by 3%. Meanwhile, the ranking of the strategies remained the same (results available on request). In the base-case analysis, we estimated treatment costs based on the guideline recommendations on the protocol treatment duration [8]. We assessed this assumption and analyzed the alteration in the cost estimates when assuming that the protocol duration equals the median treatment duration reported in the respective randomized controlled trials (Table 2). The ranking of the strategies was different in this case. However, a substantial change in the sequence costs (>10%) was noted only in case of the sequence starting with VCD (~120,000 €).

**Discussion**

Based on our analysis, the MM-related health care expenditures are mostly allocated to anticancer treatment. Costs of MM treatment and care vary substantially among the analyzed protocols. The most costly treatment protocol is RD, recommended for refractory or recurrent patients with MM. Among the routinely administered treatment options, the highest costs are estimated for treatment sequences starting with MPV. This can be explained by the fact that the first-line MPV costs are higher than the costs of bortezomib-based treatments administered as a second-line alternative to the patients who failed the upfront thalidomide-based regimens (85,200 € per protocol for the first-line MPV vs. 63,300 € per course for second-line bortezomib-based protocols on average).

In the base-case analysis, we estimated the costs of the sequential treatment alternatives under the assumption of the guideline-based treatment durations. Since this might not be the situation in the real-world setting, we tested this assumption by taking into the perspective the duration of the treatment reported in the respective studies. The resulting costs of the sequential treatments markedly differed only in case when starting with VCD. The VCD sequence costs were 33% lower due to the shortened treatment duration of both first-line VCD (from 6 to 4.5 months) and subsequent second-line MPT protocol (from 6 to 4 months).

Although there is a number of economic evaluations assessing the burden of MM [33, 36, 37], the conclu-
sions of these studies are not easily transferable to the Serbian healthcare system, due to variations in drug availability and costs and diverse patterns of treatment between the different healthcare systems. Our analysis resulted in a higher cost of bortezomib-based protocols in comparison to thalidomide- and bendamustine-based protocols for the first-line MM treatment. In the study of Garrison et al. [38], MPT and MPV protocols were compared from the perspective of the United States, where MPV protocol is shown to be less costly. However, the authors explained that the results of this comparison are strongly related to the price of thalidomide. Of note, in the United States, thalidomide is available only at a patent-protected price, while in Europe, including Serbia, generic pricing is available. Thus, the cost analyses that adopted perspectives of the European Union countries [39–41] resulted in higher costs of bortezomib-based protocols in comparison to thalidomide-based ones. Our analysis showed that the highest proportion of the healthcare expenditures for the treatment and management of MM in Serbia is allocated to drug acquisition. The proportion of total costs attributed to anti-cancer treatment in recurrent MM was 92% for lenalidomide-based regimens, 90% for bortezomib-based regimens and 54% for thalidomide-based protocols. The higher proportions of drug costs in comparison to other studies [39, 40] can be explained by the fact that the pricing of medications in Serbia is based on the European Union recommendations [42], while the unit costs of diagnostic procedures and inpatient care are significantly lower in Eastern Europe.

Our study has several limitations. In order to simplify the clinical reality, our analysis was based on several assumptions. We assumed that the effectiveness of the subsequent treatment lines is independent of the previous treatment. No dose modifications were assumed in the analysis. Clinical and methodological diversity between the studies was inevitable, considering a wide spectrum of analyzed treatment protocols. For example, variations in drug dosing and administration that exist even within a single regimen may affect the generalizability of our findings. Effectiveness estimates for chemotherapy and palliative treatment were based on the combination of evidence from clinical trials and observational studies since the data in the published randomized controlled trials were incomplete and unreliable; thus, we varied the estimates in a sensitivity analysis and the main conclusions remained the same. Data on treatment patterns and resource use in the Serbian settings are based on the national guideline recommendations, modified and precisely defined by the panel of clinical experts. Although the optimal size of the expert group in a Delphi panel is not defined [11], it would be interesting in future studies to re-analyze the estimates based on the data provided by a wider circle of clinical experts. Furthermore, validation of the findings with patient-level data would result in even more robust cost estimates. We consider the methodological approach and the results of our study generalizable to other hematologic institutions in Serbia and other similar publicly funded health care systems. However, the results of the Delphi panel that we conducted have shown that there might be individual practice variations among the oncologists of one institution, which could be even more evident across different hospital settings. Therefore, it is necessary to ensure that the recommendations of evidence-based national guidelines are followed in order to control costs, but also to provide the most beneficial patient outcomes. Based on our analysis, the most influential components of the total costs were costs of anti-cancer treatment, costs for diagnostic tests and inpatient care. Therefore, if the Serbian society that operates under the restricted healthcare budget tends to reduce the spending or reallocate the resources for management of elderly MM patients, the preferred approaches would be those reducing treatment costs and length of hospitalization. Costs of inpatient care could be reduced by redistribution of patients on injectable drugs to the less costly daily hospital or outpatient care setting. However, in elderly patients, not only costs of management of the disease but also the quality of life, travel distance to the institution and patient’s wishes should also be considered and well balanced during the decision making [43].

**Conclusion**

In conclusion, the study has revealed that the sequential strategy, which provides the most durable life-long sequential treatment, meaning concurrently the most beneficial survival outcome, is the treatment sequence starting with melphalan-prednisone-bortezomib, followed by the markedly less-costly sequence starting with melphalan-prednisone-thalidomide. The absolute difference in costs between these two strategies is 68,000 €, and the absolute difference in median sequential treatment duration is 2.5 months. A cost-effectiveness analysis, preferably employing carefully assessed quality of life for every multiple myeloma treatment protocol as an effectiveness measure, would result in more informative cost-effectiveness estimates, providing a reliable base for clinical decision making.

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