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Treatment sequences and drug costs from diagnosis to death in multiple myeloma

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Abstract

Novel therapies for multiple myeloma (MM) have improved patient survival, but their high costs strain healthcare budgets. End-of-life phases of treatment are generally the most expensive, however, these high costs may be less justifiable in the context of a less pronounced clinical benefit. To manage drug expenses effectively, detailed information on end-of-life drug administration and costs are crucial. In this retrospective study, we analysed treatment sequences and drug costs from 96 MM patients in the Netherlands who died between January 2017 and July 2019. Patients received up to 16 lines of therapy (median overall survival: 56.5 months), with average lifetime costs of €209 871 (€3111/month; range: €3942–€776 185) for anti-MM drugs. About 85% of patients received anti-MM treatment in the last 3 months before death, incurring costs of €20 761 (range: €70–€50 122; 10% of total). Half of the patients received anti-MM treatment in the last 14 days, mainly fully oral regimens (66%). End-of-life treatment costs are substantial despite limited survival benefits. The use of expensive treatment options is expected to increase costs further. These data serve as a reference point for future cost studies, and further research is needed to identify factors predicting the efficacy and clinical benefit of continuing end-of-life therapy.

KEYWORDS

clinical practice, cost, cost-effectiveness, end-of-life, multiple myeloma, terminal, treatment

Novelty Statement

What is the new aspect of your work?

While treatment patterns in multiple myeloma (MM) have been reported previously, a complete and detailed overview for all patients (i.e., follow-up until death for all patients)—and the corresponding drug costs—is absent.

M. R. Seefat and D. G. J. Cucchi contributed equally to this study.

What is the central finding of your work?

We found that drug costs are substantially higher during the end-of-life phase compared with earlier treatment phases, which may be disproportionate given the limited survival and quality of life benefits of treatment during the end-of-life.

What is (or could be) the specific clinical relevance of your work?

Our data can serve as a reference and enable comparison within future cost studies, while we also discuss several opportunities to lower drug expenses aiming for future affordability of health care.

1 | INTRODUCTION

Novel drugs for multiple myeloma (MM) meaningfully improve duration and quality of life, but are associated with high drug costs. With combination regimens being the cornerstone of MM treatment, these drug costs now represent the most important component of overall healthcare expenses in MM treatment.[1] This increasingly puts pressure on healthcare budgets,[2–8] and potentially endangers (future) access to health care.[9] Thus, sensibly utilising (expensive) drugs and applying these agents in the right patient at the appropriate time—including timely cessation of treatment—is crucial to ensure affordability, which supports the goal of achieving and retaining global drug access for MM patients.

Several studies examined treatment and the associated costs in MM patients in clinical practice,[10–12] identifying the initial 'post-diagnosis' phase and 'end-of-life' phase as being the costliest.[10,11] High drug costs during early phases are justified given that treatment efficacy is most pronounced during initial lines of therapy.[2,13–15] However, over time and especially during end-of-life, the anticipated outcomes on length and quality of life are diminished,[10,11,16–19] rendering high treatment expenses in this phase less justifiable.[20–22] Thus, adopting a prudent strategy for utilising healthcare resources during the end-of-life phase could be a helpful approach to control drug expenses in MM.

To effectively manage drug expenses, information regarding drug administration and associated drug costs during end-of-life treatment—in the context of the overall treatment trajectory—is crucial. Healthcare utilisation in MM patients during end-of-life has been studied to some extent, showing that a substantial number of patients receive chemotherapy in the last 14 days and are hospitalised in the last 30 days before dying.[23] However, data on which medications are administered and the corresponding drug costs are lacking.[10,11,23,24] In addition, while treatment patterns in daily clinical practice have been reported previously, a complete overview for all patients (i.e., follow-up until death for all patients) is absent. Finally, the definition of the end-of-life phase is not well-established and varies from the last 14 days to 12 months among studies,[10,11,23,24] providing an opportunity to explore end-of-life costs in a broader context.

To identify opportunities to optimise the end-of-life phase treatment, we systematically assessed drug usage in clinical practice for MM treatment and drug costs in a cohort of 96 MM patients from diagnosis to death. We specifically focused on drug costs in the end-of-life treatment phase, exploring various definitions of this time period. With this, we provide a platform for future studies to guide sensible medical decision-making during the end-of-life phases in particular.

2 | METHODS

2.1 | Inclusion

Adults ≥18 years with a confirmed diagnosis of MM[25] who underwent (a part of) their anti-MM treatment at Amsterdam UMC, the Netherlands, and who died between 1 January 2017 and 1 July 2019 were eligible for inclusion (Figure 1). Since this is a retrospective cohort study and no comparison is made with another cohort, we chose a uniform time period in which patients died to be able to investigate end-of-life costs. We identified patients via electronic medical records ($n = 97$) and through the Netherlands Cancer Registry ($n = 31$). Patients with missing treatment data and patients diagnosed with plasma cell leukaemia and smouldering MM were excluded ($n = 32$).

2.2 | Treatment

We extracted all sequential anti-MM treatments from diagnosis to death, including dose adjustments and start and stop dates. We stratified first-line treatment regimens based on whether patients underwent stem cell transplantation (SCT; autologous or allogeneic) in first

FIGURE 1 Inclusion criteria.

line or not. We considered induction therapy, followed by SCT and maintenance therapy, as one line of therapy. Drug treatments that were administered as part of clinical trials were included in this analysis if available.

2.3 | Costs of treatment

Drug resource use was calculated using the duration of treatment (stop date minus start date), dose adjustments, preliminary stops and temporary stops. Drug costs were calculated using fixed prices from the Z-index (which includes the publicly available list prices in the Netherlands).[26] As guidelines for economic evaluations stipulate, we chose one reference time point for list prices in this study (i.e., August 2020).[27,28] Costs of drugs that were administered as part of clinical trials were included when prices were available. For iberdomide ($n = 4$) and teclistamab ($n = 1$), no costs were yet available. Since we solely focused on drug costs, related costs of, for example, admissions, blood products and imaging are not included.

2.4 | Analyses

We analysed patient characteristics and all treatment sequences from diagnosis to death. Drug costs are reported as mean, median and range of costs from diagnosis to death, costs per treatment line and costs during various end-of-life phases (3 months, 30 days, 14 days and 7 days before death). Patients with an overall survival (OS) of less than 30 days were excluded from end-of-life analyses. The length of time of a particular treatment line was defined as the time from the start of treatment to the next treatment or death. All costs are expressed in euros per month during each line of therapy or within a specific time period before death, with reference year 2020. R-studio version 4.2.1 and packages 'highcharter' and 'ggplot2' were used for data visualisation.

3 | RESULTS

3.1 | Cohort characteristics

We identified 96 eligible patients. These patients were diagnosed with MM between 2001 and 2019. The median age at diagnosis was 63 (range: 40–83) years. Patients received a median of 5 lines of therapy (range: 1–16), regardless of whether they underwent SCT (64%; Table S1). Within the entire cohort, the median OS was 56.5 months (95% confidence Interval [CI]: 44.9–68.1 months; Table S1).

3.2 | Time to next treatment or death

The median time to the next treatment or death decreased over the lines of treatment: from 20 months between the first and second line of therapy to a median of 3.2 months from the start of the last line of therapy to death (Figure 2). Times to next treatment were comparable for patients who underwent SCT and those who did not, except for the first line of treatment (median 24.0 vs. 12.0 months).

3.3 | Overview of treatment regimens

Overall, the 96 patients received a total of 489 lines of therapy, including two-drug regimens in 200 (41%) and three-drug regimens in 270 (55%). Lenalidomide was prescribed in 173 out of 489 lines of therapy (35%), whereas pomalidomide was used in 72 of 489 lines of therapy (15%). Bortezomib was used in 136 lines of therapy (28%), carfilzomib in 37 lines of therapy (8%) and ixazomib in 6 lines of therapy (1%). Daratumumab was used in 28 out of 96 patients (29%), which occurred mostly in later lines of therapy. Of those 28 patients, 16 (57%) received daratumumab as part of clinical trial medication, of whom 9 before reimbursement in the Netherlands. Daratumumab was mainly used in combination with dexamethasone alone in 20 of 28 patients (71%), while 8 received daratumumab as part of a three-drug regimen. Sequential treatment regimens are summarised in Figure S1.

Fifty-six patients (58%) participated in at least one clinical trial. Eighty-one out of 489 (17%) lines of therapy were part of a clinical trial. In later lines of therapy, relatively more patients participated in clinical trials; from 20% (19/96 patients) in the first line of therapy to 35% (6/17 patients) in the eighth line of therapy. However, a smaller fraction of patients participated in clinical trials in the last line of therapy (9/96 patients; 9%).

3.4 | Lifetime anti-MM drug costs

The mean lifetime anti-MM drug costs—from diagnosis to death—were €209 871 (range: €3942–€776 185), equivalent to €3111 per month. First-line drug costs were similar for SCT and non-SCT patients, but as a consequence of the longer time to the next treatment, costs per month were lower: €1548 (SCT) versus €2645 (non-SCT). The mean anti-MM drug expenses per month of time to the next treatment were the lowest in the first line (€2073). However, these costs more than doubled in the second line (€4767, $n = 89$) and increased further to €8295 in the eighth line of treatment and was €6708 in the line of therapy prior to death ($n = 95$, one patient received iberdomide for which the price was not yet available) (Figure 3).

3.5 | Treatment during the end-of-life phase

Eighty-five percent of patients (80/94) received anti-MM drugs in the last 3 months preceding death. With increasing proximity to death, the proportion of patients receiving anti-MM treatment declined: 68%, 50% and 33% of patients in the last 30, 14 and 7 days preceding

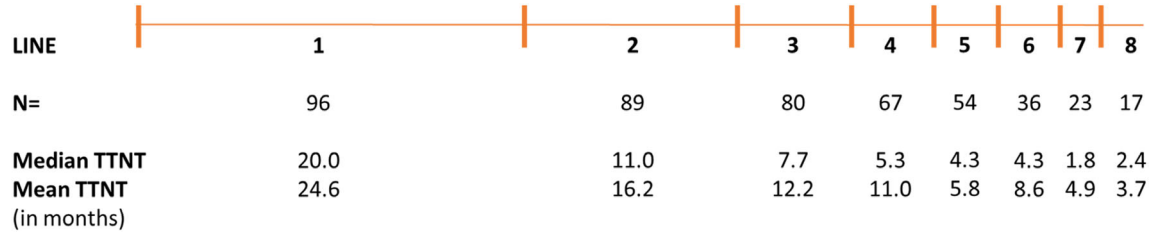

FIGURE 2 Time to next treatment or death (TTNT) for each line of therapy for all patients.

FIGURE 3 Mean costs per patient per month per line of therapy.

TABLE 1 First-line treatment regimens.

	SCT[a] ($n = 50$)	No SCT ($n = 46$)
Single-drug regimen	0 (0%)	1 (2.2%)
Two-drug regimen	2 (4%)	10 (21.7%)
Three-drug regimen	48 (96%)	35 (76.1%)
Bortezomib induction/ regimen	27 (54%)	28 (60.9%)
MPV	0	9 (19.6%)
Vd	2 (4%)	6 (13%)
VCD	19 (38%)	6 (13%)
VTD	4 (8%)	6 (13%)
Others	23 (46%)	18 (39.1%)
Maintenance therapy containing	13 (26%)	
Lenalidomide	7 (14%)	1 after VCD/MPV (2.2%)
Thalidomide	4 (8%)	

Abbreviations: MPV, melphalan–prednisone–bortezomib; SCT, stem cell transplantation; VCD, bortezomib–cyclophosphamide–dexamethasone; VD, bortezomib–dexamethasone; VTD, bortezomib–thalidomide–dexamethasone.
[a]In first line of treatment.

death, respectively (Table 2). Within the last 3 months, 30 patients (32%) initiated a new treatment regimen, with 7 of 30 (23%) switching to a second regimen within this period. Of the patients who started a new anti-MM treatment within 3 months preceding death, 13 patients

TABLE 2 Overview of treatment regimens in second and third line.

Treatment	Second line ($n = 89$)	Third line ($n = 80$)
SCT	19 (21.4%)	7 (8.8%)
Single-drug regimen	3 (3.4%)	2 (2.5%)
Two-drug regimen	55 (62.9%)	37 (46.2%)
Three-drug regimen	30 (33.7%)	41 (51.3%)
Lenalidomide	58 (65.2%)	43 (53.8%)
Pomalidomide	3 (3.4%)	10 (12.5%)
Bortezomib	23 (25.8%)	23 (28.8%)
Carfilzomib	14 (15.7%)	3 (3.8%)
Daratumumab	1 (1.1%)	3 (3.8%)

Abbreviation: SCT, stem cell transplantation.

(13/30; 43%) initiated a new treatment within the last 30 days, and 7 of those (7/30; 23%) started within the last 14 days. No new regimens were initiated within 7 days preceding death. The median time between the last day of anti-MM treatment and death was 14 days (range: 0–3087) (Table 1). The median duration of the last anti-MM treatment regimen was 74 days (2.4 months, range: 1–2050 days).

Of the patients who received therapy in the last 3 months ($N = 80$), 58% ($N = 46$) received parental drugs and 42% ($N = 34$) received a fully oral treatment regimen. Treatment regimens in the last 7 days preceding death were mostly fully oral regimens (70% [24/31]). Oral regimens in the last 3 months and 7 days consisted of lenalidomide (38% [30/80] and 13% [4/31], respectively), pomalidomide (46% [37/80] and 42% [13/31], respectively) and cyclophosphamide (61% [49/80] and 65% [20/31], respectively). Parenteral drugs bortezomib, carfilzomib and daratumumab in the last period before death were 11% (9/80), 24% (19/80) and 23% (18/80) in the last 3 months to 0% (0/31), 13% (4/31) and 3% (1/31), respectively, in the last 7 days (Table S2).

3.6 | Drug costs during end-of-life

During the last 3 months before death, mean anti-MM drug costs were €20 761 (range: €70–€50 122), accounting for 10% of total mean drug costs, whereas the last 3 months accounted for 4% of the mean OS (67.4; range: 58.1–76.7 months) (Table S1). Drug costs per month remained approximately similar during end-of-life phases,

TABLE 3 Drug costs of myeloma treatment per treatment phase.

Treatment phase	Patients receiving treatment (% of total)	Mean costs of treatment (range; % of total costs)	Mean relative costs per month[a]
Diagnosis to death	96	€209 871 (€3942–€776 185; 100)	€3111[b]
First line of treatment	96	€38 770 (€70–€497 637; 18.5)	€2073
SCT	50 (52.0)	€37 262 (€2226–€242 721; 17.8)	€1548
No SCT	46 (48.0)	€40 410 (€70–€497 637; 19.3)	€2645
Second line until death	89 (92.7)	€184 558 (€3873–€751 849; 87.9)	€5180
3 months before death	80 (85.1[c])	€20 761 (€70–€50 122; 9.9)	€6920
30 days before death	64 (68.1[c])	€6212 (€10–€17 444; 3.0)	€6295
14 days before death	47 (50.0[c])	€3006 (€9–€9512; 1.4)	€6527
7 days before death	31 (33.0[c])	€1642 (€3–€4757; 0.8)	€7131

[a]One month is defined as 30.4 days.
[b]Mean total costs divided by mean OS in months.
[c]Ninety-four patients were included in end-of-life analysis, two patients were excluded because of a survival of less than 30 days from diagnosis.

ranging from €6295 to €7131 per month (Table 3). The highest drug costs in the last 3 months were associated with more recently introduced drugs (i.e., daratumumab or pomalidomide). The mean drug costs in the final 7 days were €1642, ranging from €3 to €4757.

4 | DISCUSSION

With this study, we provide unique clinical practice data on the use and cost of anti-MM drugs from diagnosis to death, with emphasis on 'end-of-life' treatment. Unlike previous studies, which relied on health insurance databases, our study used patient-level health record data, and specifically focused on drug costs. We found that a notably higher percentage of patients received active treatment in the last 30, 14 and 7 days before death (68%, 50% and 33%, respectively) compared with previous studies (in which 23% of patients received chemotherapy during the last 14 days).[23] This is important, as monthly drug costs of this limited extension of lifespan (extension) were twice as high as the average monthly overall lifetime drug costs, with the last 3 months constituting 10% of the total lifetime drug costs.

We found that anti-MM drug costs were markedly higher than previously reported: the monthly drug costs were €6920 in the final 3 months of life, compared with $1847 (€1729; using the SDR per currency unit on 1 March 2023, International Monetary Fund[29]) attributed to 'prescription drugs' by a previous study.[10] The mean costs in the last 30 days of €6212 were also higher than recently reported in a (non-academic) monocentral study in the Netherlands (€1614).[24] All of our patients received treatment (in part) within an academic hospital, which may have contributed to a higher number of patients receiving active treatment during end-of-life. It is possible that the selection of patients treated within an academic hospital resulted in a higher preference for extending life compared with patients in non-academic regional hospitals. In addition, our study included patients who were treated in clinical trials. These clinical trials involved the use of non-reimbursed drugs, and the estimated costs of such drugs, if used in clinical practice, were included in our analysis.

One might argue that newer and costlier drugs—such as daratumumab and carfilzomib—were prescribed only limitedly in our cohort, and therefore, our cost analysis does not reflect the current treatment landscape. Indeed, we anticipate that such costlier drugs will be used increasingly extensively, as well as in earlier lines of therapy. Subsequently, the cost of drugs for MM treatment will increase far beyond what we outlined in this study. However, we anticipate that the cost distribution, with higher costs in later lines of therapy, will remain similar. If there are any differences, we expect the costs of later lines of therapy to increase rather than decrease. As an example, novel T-cell immunotherapies, such as T-cell redirecting bispecific antibodies and CAR-T cells, are currently being used in later lines of therapy, with considerable costs.[30–33] Therefore, our findings can serve as a reference which will enable comparisons with future cost studies in order to follow-up on the budget impact of novel drug development on a national level.

Our data indicate that monthly anti-MM drug costs increase with subsequent lines of therapy, with end-of-life costs constituting 10% of the total drug costs. Importantly, the cost of orally dispensed drugs during end-of-life might be even higher since more oral drugs might have been prescribed than captured: we only included costs of drugs that patients could have used in their lifespan. The significant financial burden of active anti-MM treatment during end-of-life may not be justifiable as we presume that the gain in quality of life is minimal during end-of-life: disease control will be limited, and MM-related symptoms negatively affect the quality of life.[21,22,34,35] Thus, our data stress the necessity to discuss whether active treatment during end-of-life is desirable, and hint at several opportunities to optimise drug treatment during end-of-life and mitigate associated drug costs.

In general, physicians should prescribe active anti-MM treatments cautiously during the end of life, only in the presence of sufficient evidence that such drugs will provide benefits for both quantity and

quality of life. In line with this, beginning at an early stage, physicians should continuously assess the patient's preference for sustained treatment in case the end-of-life approaches, especially as we and others showed that the time to the next treatment generally decreases with each new line of therapy.[2,36] Such advanced care planning improves quality of life and reduces symptom burden in cancer patients—independently of active treatment—while it reduces overall cost.[37] Specific to the use of oral drugs—although challenging from a logistical and regulatory perspective—the redistribution of unused oral drugs is feasible and could result in substantial cost savings and is desirable from a sustainability perspective.[38]

Perhaps most importantly, physicians need tools to predict the approach of end-of-life and help them differentiate between patients who will benefit from continued active treatment and those patients who would be better served by supportive care. Our data indicate that a substantial percentage of patients receive active treatment in close vicinity of death, and although previous studies identified predictors for early mortality,[39,40] data to predict death at later stages are lacking. Therefore, future studies investigating predictive factors for death during end-of-life treatment are eagerly needed as these can aid in preventing the administration of non-beneficial treatments for patients and society as a whole. National and international population-based registries should collect real-world data on length and quality of life in combination with drug use to facilitate such analyses. To analyse the costs of drug treatment, the use of true prices instead of list prices is essential for data accuracy. The latter is only possible if complete transparency is provided by negotiating parties, which will remain a hurdle for future studies. We anticipate that integrative analyses of drug cost and effectiveness will furnish valuable instruments for enhancing cancer care and quality of life while reducing the financial impact of MM treatment.

5 | CONCLUSION

Active treatment is prescribed to half of all MM patients in this study in the last 2 weeks before death, and the associated drug costs may not be justified by the resulting clinical benefit. A proper balance between clinical benefit, patient preferences and economic sustainability can only be achieved when there is sufficient evidence to identify those patients who will benefit from continued treatment and taking into account the relation between the benefits and costs (i.e., cost-effectiveness) of such treatment into account. Future studies require detailed data from real-world registries to combine patient-level characteristics, survival and quality of life data with true drug prices and usage, to inform physicians and healthcare policymakers. Such studies are urgently needed to ensure access and sustainability to health care in the future.

AUTHOR CONTRIBUTIONS

M. R. Seefat, D. G. J. Cucchi, K. Groen, M. L. Donker, N. W. C. J. van de Donk, H. M. Blommestein and S. Zweegman participated in the design of this analysis. M. R. Seefat, D. G. J. Cucchi, K. Groen, M. L. Donker, N. W. C. J. van de Donk, H. M. Blommestein and S. Zweegman participated in data analysis. All authors contributed to data collection and participated in writing the article.

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CONFLICT OF INTEREST STATEMENT

S. Zweegman has received research funding from Celgene, Takeda and Janssen, all paid to their institution; and serves on advisory boards for Janssen, Takeda, Bristol Myers Squibb, Oncopeptides and Sanofi, all paid to their institution. H. M. Blommestein reports consulting role for Pfizer and research funding from BMS-Celgene, all paid to the institute. N. W. C. J. van de Donk has received research support from Janssen Pharmaceuticals, AMGEN, Celgene, Novartis, Cellectis and BMS, all paid to their institution; and serves in advisory boards for Janssen Pharmaceuticals, AMGEN, Celgene, BMS, Takeda, Roche, Novartis, Bayer, Adaptive and Servier. D. G. J. Cucchi received payments for lectures for Takeda, and conference visit support from Servier, all outside the submitted work. Other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author.

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REFERENCES

1. Choon-Quinones M, Zelei T, Barnett M, et al. Beyond medicines' barriers: exploring the true cost of multiple myeloma. *J Med Econ*. 2022; 25(1):1167-1175.
2. van de Donk N, Pawlyn C, Yong KL. Multiple myeloma. *Lancet*. 2021; 397(10272):410-427.
3. Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia*. 2017;31(9): 1915-1921.
4. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5): 2516-2520.
5. Braunlin M, Belani R, Buchanan J, Wheeling T, Kim C. Trends in the multiple myeloma treatment landscape and survival: a U.S. analysis using 2011-2019 oncology clinic electronic health record data. *Leuk Lymphoma*. 2021;62(2):377-386.
6. Jagannath S, Joseph N, He J, et al. Healthcare costs of multiple myeloma patients with four or more prior lines of therapy, including triple-class exposure in the United States. *Oncol Ther*. 2022;10(2): 411-420.

7. Dusetzina SB, Huskamp HA, Qin X, Keating NL. Prescription drug spending in fee-for-service Medicare, 2008-2019. *JAMA*. 2022; 328(15):1515-1522.
8. Neves M, Trigo F, Rui B, et al. Multiple myeloma in Portugal: burden of disease and cost of illness. *Pharmacoeconomics*. 2021;39(5): 579-587.
9. Seefat MR, Cucchi DGJ, Dirven S, Groen K, Zweegman S, Blommestein HM. A systematic review of cost-effectiveness analyses of novel agents in the treatment of multiple myeloma. *Cancers*. 2021; 13(22):5606.
10. Bhattacharya K, Bentley JP, Ramachandran S, et al. Phase-specific and lifetime costs of multiple myeloma among older adults in the US. *JAMA Netw Open*. 2021;4(7):e2116357.
11. de Oliveira C, Pataky R, Bremner KE, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. *BMC Cancer*. 2016;16(1):809.
12. Maiese EM, Evans KA, Chu BC, Irwin DE. Temporal trends in survival and healthcare costs in patients with multiple myeloma in the United States. *Am Health Drug Benefits*. 2018;11(1):39-46.
13. Paul B, Lipe B, Ocio EM, Usmani SZ. Induction therapy for newly diagnosed multiple myeloma. *Am Soc Clin Oncol Educ Book*. 2019;39: e176-e186.
14. Lahuerta JJ, Paiva B, Vidriales MB, et al. Depth of response in multiple myeloma: a pooled analysis of three PETHEMA/GEM clinical trials. *J Clin Oncol*. 2017;35(25):2900-2910.
15. Mateos MV, San Miguel JF. Management of multiple myeloma in the newly diagnosed patient. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):498-507.
16. Reeve R, Srasuebkul P, Langton JM, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. *BMC Palliat Care*. 2017;17(1):1.
17. Chastek B, Harley C, Kallich J, Newcomer L, Paoli CJ, Teitelbaum AH. Health care costs for patients with cancer at the end of life. *J Oncol Pract*. 2012;8(6):75s-80s.
18. Wong A, van Baal PH, Boshuizen HC, Polder JJ. Exploring the influence of proximity to death on disease-specific hospital expenditures: a carpaccio of red herrings. *Health Econ*. 2011;20(4):379-400.
19. Abbasi S, Roller J, Abdallah AO, et al. Hospitalization at the end of life in patients with multiple myeloma. *BMC Cancer*. 2021;21(1):339.
20. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol*. 2016;175(2):252-264.
21. Despiégel N, Touboul C, Flinois A, et al. Health-related quality of life of patients with multiple myeloma treated in routine clinical practice in France. *Clin Lymphoma Myeloma Leuk*. 2019;19(1):e13-e28.
22. Engelhardt M, Ihorst G, Singh M, et al. Real-world evaluation of health-related quality of life in patients with multiple myeloma from Germany. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):e160-e175.
23. Mohyuddin GR, Sinnarajah A, Gayowsky A, Chan KKW, Seow H, Mian H. Quality of end-of-life care in multiple myeloma: a 13-year analysis of a population-based cohort in Ontario, Canada. *Br J Haematol*. 2022;199(5):688-695.
24. Bennink C, Westgeest H, Schoonen D, et al. High hospital-related costs at the end-of-life in patients with multiple myeloma: a single-center study. *HemaSphere*. 2023;7(6):e913.
25. Rajkumar SV. Updated diagnostic criteria and staging system for multiple myeloma. *Am Soc Clin Oncol Educ Book*. 2016;35:e418-e423.
26. Z-index. G-standaard medicijnkosten (8-2020). Z-Indexnl. 2020.
27. Nederlands Zorginstituut (Dutch Healthcare Institute). Guideline for economic evaluations in healthcare. 2016 https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare
28. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford University Press; 2015.
29. International Monetary Fund. SDRs per Currency Unit for March 2023. 2023 https://www.imf.org/external/np/fin/data/rms_mth.aspx?SelectDate=2023-03-31&reportType=SDRCV
30. Kapinos KA, Hu E, Trivedi J, Geethakumari PR, Kansagra A. Cost-effectiveness analysis of CAR T-cell therapies vs antibody drug conjugates for patients with advanced multiple myeloma. *Cancer Control*. 2023;30:10732748221142945.
31. Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2022;387(6):495-505.
32. Gagelmann N, Sureda A, Montoto S, et al. Access to and affordability of CAR T-cell therapy in multiple myeloma: an EBMT position paper. *Lancet Haematol*. 2022;9(10):e786-e795.
33. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med*. 2022;387(24):2232-2244.
34. Jordan K, Proskorovsky I, Lewis P, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. *Support Care Cancer*. 2014;22(2):417-426.
35. Fonseca R, Tran D, Laidlaw A, et al. Impact of disease progression, line of therapy, and response on health-related quality of life in multiple myeloma: a systematic literature review. *Clin Lymphoma Myeloma Leuk*. 2023;23:426-437.e11.
36. Verelst SGR, Blommestein HM, De Groot S, et al. Long-term outcomes in patients with multiple myeloma: a retrospective analysis of the Dutch Population-based HAematological Registry for Observational Studies (PHAROS). *HemaSphere*. 2018;2(4):e45.
37. Klingler C, in der Schmitten J, Marckmann G. Does facilitated advance care planning reduce the costs of care near the end of life? Systematic review and ethical considerations. *Palliat Med*. 2016;30(5):423-433.
38. Bekker CL, Melis EJ, Egberts ACG, Bouvy ML, Gardarsdottir H, van den Bemt BJF. Quantity and economic value of unused oral anticancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy. *Res Social Adm Pharm*. 2019;15(1):100-105.
39. McQuilten Z, Wellard C, Moore E, et al. Predictors of early mortality in multiple myeloma: results from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR). *Br J Haematol*. 2022;198(5):830-837.
40. Terebelo H, Srinivasan S, Narang M, et al. Recognition of early mortality in multiple myeloma by a prediction matrix. *Am J Hematol*. 2017; 92(9):915-923.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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