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Multiple Myeloma: Current Clinical Landscape and Compounding Costs

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Abstract

Purpose of Review The treatment landscape of multiple myeloma (MM) has evolved resulting in MM becoming a chronic condition. The costs of MM therapies are substantial and compound as patients remain on long-term maintenance therapies and progress through multiple lines of high-cost therapies. MM predominantly impacts the elderly population insured by Medicare; here, we analyze how these costs impact patients and the Medicare trust fund.

Recent Findings With the recent passing of the Inflation Reduction Act (IRA), we postulate how costs may be impacted and debate future policy initiatives that may result in sustainability.

Summary The IRA will impact drug pricing and likely reduce the costs of some treatments used in MM; there is still a lot of room for policy reform to reduce financial toxicity to patients and prevent depletion of the Medicare trust fund.

Keywords Multiple myeloma · Financial toxicity · Medicare · Inflation Reduction Act

Introduction

Multiple myeloma (MM) is a neoplasia of plasma cells, which consists of a plasma cell evolving into a premalignant monoclonal gammopathy of uncertain significance, followed by smoldering myeloma, and then arising as multiple myeloma that requires treatment [1•]. MM is the second most common hematological malignancy, and it accounts for 1–1.8% of all cancers [2•]. There have been many recent advances in multiple myeloma treatment, causing MM to shift from a life-ending malignancy to a chronic condition that patients can live with for years.

In the early 1990s, MM treatment consisted of a combination of melphalan, an alkylating agent, and prednisone, with a 50% treatment response rate and 25% 5-year-survival rate. In 1995, stem cell transplantation increased the 5-year-survival rate to 50%. The next major advancement in treatment occurred in 2003 with the release of bortezomib, a proteasome inhibitor. With many developments since then, current treatment regimens consist primarily of 3- and 4-drug regimens, chimeric antigen receptor therapy (CAR-T) cell therapy, and bispecific antibody therapies. First-line drug regimens typically consist of proteasome inhibitors, second- and third-generation immunomodulatory drugs, and steroids with or without monoclonal antibodies [3•]. More specifically, in patients who are eligible for autologous stem cell transplants, a typical three-drug induction therapy includes lenalidomide, bortezomib, and dexamethasone for 3–4 cycles prior to their transplant. For patients with higher risk disease, daratumumab an anti-CD38 monoclonal antibody is commonly used. Patients who are not transplant eligible may utilize the 3- or 4-drug therapy for 8–12 cycles followed by maintenance therapy with lenalidomide, along with bortezomib for high-risk patients [4•].

With these advances in treatment, MM has become a chronic condition, with the survival rate more than

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quadrupling since the 1990s [3•]. However, life-extending treatments come with a price that many patients and their families struggle to afford. The median patient age at time of MM diagnosis is 65 years and findings from Warren and colleagues found that 72.1% of patients had private insurance, 12.9% had Medicare only, and 9.3% of patients were insured by Medicaid [4•, 5••]. In 2022, 48% of patients eligible for Medicare were enrolled in a Medicare Advantage Plan (private insurance) accounting for $427 billion (55%) of total Medicare spending [6]. The drug combination regimens emerge with immense list prices, creating concern for the long-term healthcare system burden and its impact on the Medicare trust fund [7••]. This financial strain can affect access to care, as a state of financial toxicity can develop with patients refusing certain treatments due to concern of burden on their family and financial well-being. This becomes increasingly relevant as MM is primarily present in the elderly population who have a fixed income and who face high out-of-pocket (OOP) costs even with the assistance of insurance and grants.

In this review article, we evaluate the current financial landscape of various therapies used in MM to better understand the impacts on the Medicare trust fund (Part B and Part D) and financial impacts on patients. We model two treatment pathways, transplant eligible and transplant ineligible; duration of observed benefit based on published data; and the impact of therapy costs to the Medicare trust fund as a patient progresses through multiple lines of therapy. Finally, we postulate how the Inflation Reduction Act (IRA) may impact costs and debate future policy changes that may reduce costs and improve access to care.

Current Economic Landscape

MM treatment has advanced significantly in the last 30 years, and conversations become less concerned with survival and more focused on the most appropriate long-term treatment and the financial ability of patients to afford their therapies. The National Comprehensive Cancer Network (NCCN) guidelines are a commonly referenced resource for providers supported by evidence-based medicine. While many other cancers have well-defined recommendations for specific lines of therapy, for MM, there is not a clear-cut path for which treatment is best in which line of therapy as many treatments carry category 1 endorsements. Tables 1 and 2 show the framework of various treatment options commonly used in MM for transplant-eligible and transplant-ineligible patients with dosing and wholesale acquisition costs (WAC) based on an 80 kg and 1.75-m^2 patient rounded to the nearest milligram and whole dollar. Recognizing that treatment decisions are patient and disease specific, Fig. 1 summaries treatment option pathways for a transplant-eligible and transplant-ineligible patient, median progression-free survival for each line of therapy based on clinical trials leading to their FDA approval, and associated WAC. Subcutaneous (SQ) daratumumab was used throughout Tables 1 and 2 and Fig. 1 due to similar pricing and presumed higher use in clinical practice due to chair time savings and patient convenience for SQ compared to intravenous (IV) daratumumab. Dexamethasone costs were excluded from the tables and figures due to generic availability and low cost.

Annualized WACs for first-line treatments range from $183,792 for bortezomib, lenalidomide, and dexamethasone (VRD) to $382,058 for daratumumab, lenalidomide, and dexamethasone (DRD) (Table 1). Prior studies concluded that daratumumab would need to be discounted by 67% to be cost-effective in the first-line setting using a $150,000 per quality-adjusted life year (QALY) [8••]. Costs for second-line treatments range from $203,018 for daratumumab, bortezomib, and dexamethasone (DVD) to $525,277 for daratumumab, carfilzomib, and dexamethasone (DKD), and third-line treatments range from $9,360 for oral cyclophosphamide, bortezomib, and dexamethasone (CyBorD) to $410,444 for elotuzumab, pomalidomide, and dexamethasone (EPD) (Tables 1 and 2). Costs differ based on number of cycles administered and for year one versus year two and beyond for certain regimens due to loading doses commonly utilized in the first treatment year (Tables 1 and 2). When patients get to third and later lines of therapy, there is less evidence-based medicine supporting one course over another, it is common to revisit regimens that may have been used in an earlier setting, and most therapies are priced exceedingly high [9]. For instance, the newest CAR T-cell therapies are idecabtagene vicleucel (ide-cel, Abecma) and ciltacabtagene autoleucel (cilta-cel, Carvykti), approved in the fifth-line setting in 2021 and 2022 which are currently priced at $458,185 and $465,930 per treatment respectively (Table 2, Fig. 1) [10•, 11•]. Teclistamab-cqyv (Tecvayli) is an anti-B-cell maturation antigen (BCMA)–directed therapy that gained FDA approval in 2022 in the fifth-line setting and costs $436,836 annually including billed waste (Table 2) [12••].

It is interesting to note that the costs of later-line therapies are higher without substantial survival benefit. Figure 1 demonstrates this with a 1.7- and 2.2-fold increase in cost between first- and fourth-line treatments for transplant-eligible and transplant-ineligible pathways respectively. Fifth- and later-line treatments including CAR-T and teclistamab-cqyv are priced higher than most earlier-line treatment regimens.

While patient survival has greatly increased with these therapies, challenges from the prices of drugs and patients' ability to pay are being increasingly highlighted. While these prices are like other cancer therapies, the fact that MM requires multiple drugs and lines of therapy, often receiving treatment indefinitely as maintenance treatment, causes costs to compound exponentially (Fig. 1).

Table 1 Front-line drug regimens in multiple myeloma and associated costs [29]

Patient type	Regimen	Schedule	Cost (WAC) [29]	Cost per cycle	Annual cost		Patient responsibility
Transplant eligible	DaraVRD* [30]	Induction (4 cycles): Daratumumab: days 1, 8, and 15 of a 3-week cycle for cycles 1–4 Bortezomib: 1.3 mg/m^2 days 1, 4, 8, and 11 Lenalidomide: 25 mg days 1–14 of 21 day cycle Dexamethasone: 20 mg days 1, 2, 8, 9, 15, and 16 Post-transplant consolidation: Dara-VRD cycles 5–6 (daratumumab day 1, VRD see induction dosing) Maintenance C7 + : Dara every 4 weeks Lenalidomide: 10 mg daily days 1–21 of 28-day cycle	Darzalex Faspro: $9119 per 1800–30,000 mg/15-mL vial Bortezomib 3.5 mg: $75 per vial Lenalidomide (generics): WAC $720/capsule	Induction: Darzalex Faspro: $27,357 Bortezomib: $196 Lenalidomide: $10,080 Consolidation: Darzalex Faspro: $9119 Bortezomib: $196 Lenalidomide: $10,080 Maintenance: Darzalex Faspro: $9119 Lenalidomide: $15,120	Induction (4 cycles): $150,532 Consolidation (C5–6): $38,790 Maintenance (6 cycles): $145,434 Year 1 total: $334,756		Induction, consolidation and maintenance (12 cycles) Part B: $36,711 Part D: $30,240 Maintenance costs (up to 2 years): Part B: $21,886 Part D: $36,288
	VRD [31]	Bortezomib: 1.3 mg/m^2 weekly Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Bortezomib 3.5 mg: $75 per vial Lenalidomide (generics): WAC $720/capsule	Bortezomib: $196 Lenalidomide: $15,120	$183,792		Part B: $470 Part D: $36,288
	KRD [32, 33]	Carfilzomib: 20 mg/m^2 days 1–2 (cycle 1), 27 mg/m^2 days 8–9, 15–16 (and all subsequent doses) Lenalidomide: 25 mg days 1–21 of 28-day cycle Dexamethasone: 40 mg weekly #Alternative Dosing Carfilzomib: 20 mg/m^2 day 1 (cycle 1), 56 mg/m^2 days 8, 15 (and all subsequent doses) Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Carfilzomib: WAC $49.65/mg Lenalidomide (generics): WAC $720/capsule	Carfilzomib: C1: $12,812 C2–12: $14,004 C13 + : $9336 Lenalidomide: $15,120 Alternate carfilzomib: C1: $11,470 C 2 + : $14,598	Year 1: Traditional carfilzomib: $348,296 Alternate carfilzomib: $353,488	Year 2: Traditional carfilzomib: $293,472 Alternate carfilzomib: $356,616	Traditional carfilzomib: Year 1: Part B: $33,371 Part D: $36,288 Year 2 and beyond: Part B: $22,406 Part D: $36,288 Alternate carfilzomib: Year 1: Part B: $34,410 Part D: $36,288 Year 2 and beyond: Part B: $35,035 Part D: $36,288

Table 1 (continued)

Patient type	Regimen	Schedule	Cost (WAC) [29]	Cost per cycle	Annual cost		Patient responsibility
Non-transplant eligible	VRD* [31]	Bortezomib: 1.3 mg/m^2 weekly Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Bortezomib 3.5 mg: $75 per vial Lenalidomide (generics): WAC $720/capsule	Bortezomib: $196 Lenalidomide: $15,120	$183,792		Part B: $470 Part D: $36,288
	VRD Lite [34]	Bortezomib: 1.3 mg/m^2 days 1, 8, 15, 22 Lenalidomide: 15 mg days 1–21 Dexamethasone: 20 mg weekly	Bortezomib 3.5 mg: $75 per vial Lenalidomide (generics): WAC $720/capsule	Bortezomib: $196 Lenalidomide: $15,120	$183,792		Part B: $470 Part D: $36,288
	DRD* [35]	Daratumumab: days 1, 8, 15, 22 (cycles 1–2), days 1 and 15 (cycles 3–6), every 28 days (cycle 7+) Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Darzalex Faspro: $9119 per 1800–30,000 mg/15-mL vial Lenalidomide (generics): WAC $720/capsule	Darzalex Faspro: C1–C2: $36,476 C3–6: $18,238 C7+: $9119 Lenalidomide: $15,120	Year 1: $382,058	Year 2: $290,868	Year 1: Part B: $40,124 Part D: $36,288 Year 2 and beyond: Part B: $21,886 Part D: $36,288
	KRD [32, 33]	Carfilzomib: 20 mg/m^2 days 1–2 (cycle 1), 27 mg/m^2 days 8–9, 15–16 (and all subsequent doses) Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly #Alternative Dosing Carfilzomib: 20 mg/m^2 day 1 (cycle 1), 56 mg/m^2 days 8, 15 (and all subsequent doses)	Carfilzomib: WAC $49.65/mg Lenalidomide (generics): WAC $720/capsule	Traditional Carfilzomib: C1: $12,812 C2–12: $14,004 C13+: $9336 Lenalidomide: $15,120 Alternate carfilzomib: C1: $11,470 C 2+: $14,598	Year 1: Traditional carfilzomib: $348,296 Alternate carfilzomib: $353,488	Year 2: Traditional carfilzomib: $293,472 Alternate carfilzomib: $356,616	Traditional carfilzomib: Year 1: Part B: $33,371 Part D: $36,288 Year 2 and beyond: Part B: $22,406 Part D: $36,288 Alternate carfilzomib: Year 1: Part B: $34,410 Part D: $36,288 Year 2 and beyond: Part B: $35,035 Part D: $36,288
	DaraCyBorD [36, 37]	Daratumumab: days 1, 8, 15, 22 (cycles 1–2), days 1 and 15 (cycles 3–6), every 28 days (cycle 7+) Cyclophosphamide: 300 mg/m^2 days 1, 8, 15, 22 Bortezomib: 1.3 mg/m^2 days 1, 8, 15, 22 Dexamethasone: 40 mg weekly	Darzalex Faspro: $9119 per 1800–30,000 mg/15-mL vial Bortezomib 3.5 mg: $75 per vial Cyclophosphamide IV: $0.37 per mg Cyclophosphamide PO: (dispense 10×50 mg ($13.75 each) and 1×25 mg ($7.49 each)) $145	Darzalex Faspro: C1–C2: $36,476 C3–6: $18,238 C7+: $9119 Cyclophosphamide IV: $777 PO: $580 Bortezomib: $200	Using IV cyclophosphamide: $212,342 Using PO cyclophosphamide: $209,978		Using IV cyclophosphamide: Part B: $42,468 Using PO cyclophosphamide: Part B: $40,604 Part D: $1392
	IRD [38]	Ixazomib: 4 mg once weekly days 1, 8, 15 Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Ixazomib: $12,240 Lenalidomide (generics): WAC $720/capsule	Ixazomib: $12,240 Lenalidomide: $15,120	$328,320		Part D: $65,664

*Category 1 NCCN v3.23; *WAC* wholesale acquisition cost, *IV* intravenous, *PO* oral

The Kaiser Family Foundation notes that 5.6 million beneficiaries in traditional Medicare have no supplemental coverage [13••]. Patients enrolled in a Medicare Advantage Plan (MAP) have an OOP maximum of $7,550 for in-network cost sharing and $11,300 for in-network and out-of-network cost sharing combined in 2022 [14••]. Despite having Medicare or other insurance coverage, there still is significant coverage gap that patients must manage. Medicare Part D currently does not have a hard cap on OOP spending. As of 2023, OOP spending threshold increased from $7,050 to $7,400. When $7,400 OOP is reached and patients have spent a total of $11,206 including deductibles, enrollees within the catastrophic coverage threshold continue to pay 5% OOP, with 80% covered by Medicare and 15% covered by insurance plans. Patients in the catastrophic threshold will continue to pay 5% of the total drug cost, or $4.15 or $10.35 for each generic or brand drug respectively [15••]. For regimens that include lenalidomide and pomalidomide, annual costs mount to $181,400 and $235,476 annually for Part D alone (Tables 1 and 2). Using the 2023 Medicare pricing structure, patients will exceed their OOP maximum in the second or third fill of the year and remain responsible for $756 OOP for lenalidomide and $1056 for pomalidomide with Medicare covering the remaining $12,096 and $16,898 respectively per month [15••]. In total, for patients with traditional Medicare on a regimen containing lenalidomide and pomalidomide, assuming they reach catastrophic coverage phase after the second fill of the year and that their responsibility would be 5% of cost once in the catastrophic phase, the cumulative annual OOP expense for patients would mount to $18,766 and $21,766 for lenalidomide and pomalidomide regimens respectively.

According to a survey of 111 MM patients in 2015, 71% reported financial burden [16•]. This burden was attributed not just to medications but also hospital stays and doctor's visits that accumulate when living with a chronic disease [16•]. The IRA will limit Part D OOP costs to $2000 in 2025 and the Medicare trust fund will shoulder more of this financial burden [17••]. Given pomalidomide and lenalidomide are in the same drug class, Medicare could choose to exclude pomalidomide from formularies which may hinder access to care in treatment refractory patients [15••].

For Medicare Part B, enrollees are responsible for 20% of the cost based on the Medicare allowable amount average selling price (ASP) + 6% or ASP + 8% of reference product's ASP for biosimilars. Patients enrolled in traditional Medicare do not have an annual OOP limit for Medicare Part B. For MM patients with traditional Medicare and no Medigap coverage policy, Tables 1 and 2 describe the exceedingly large amount of OOP spent on Medicare Part B. For patients enrolled in a MAP plan, Tables 1 and 2 illustrate again that patients will reach their OOP maximum quickly in the beginning of the year with the Medicare trust fund covering a vast majority of remaining costs.

Significant Trends and Developments

Discussions about price control are necessary as options for future treatments are already underway. CAR-T therapies and bispecifics are being studied in earlier lines of therapy; however, costs would be further compounded if these agents are re-considered during a later line of therapy when a patient relapses. With value-based arrangements being a newer concept, it is unclear if Medicare would be able to negotiate such agreements with manufacturers and who would be responsible for tracking outcomes.

Moreover, there has been a mention of molecularly targeted agents that function specific to a patient's disease to ensure efficacy and decrease the risk of toxicity. The understanding of myeloma on a molecular level is continually growing, and studies have shown that MM lesions could be selectively targeted based on a high cancer clonal fraction. This novel therapy could be used in combination with current therapies, supporting that many treatment advancements are anticipated in the near future. Thus, it is essential for patients, researchers, manufacturing companies, and all other stakeholders to reach an agreement that is affordable for consumers while remaining profitable for those in production, so novel therapies can continue to be introduced and provide benefit to the population [1•].

Discussion

The current economic landscape is further complicated by the fact that pharmaceutical companies tend to price their new drugs based upon what is currently available in the market and increase costs at a similar rate to competitors, a term known as shadow pricing [18••]. There have also been accusations that these companies reformulate drugs with an expanded patent termed product hopping, so patients can be switched to the new drug and their market monopoly continues [19•]. Daratumumab SQ was utilized throughout Tables 1 and 2 and Fig. 1 as it offers significant chair time savings to infusion centers and resultantly patient convenience, but this is an example of product hopping as IV daratumumab will lose patent exclusivity in 2029 and SQ daratumumab loss of patent exclusivity expiration is not well understood [20•]. It will be challenging for infusion centers and patients alike to transition to a daratumumab IV biosimilar once patent exclusivity expires. Moreover, extending patents through evergreening and patent thickets extend a company's monopoly, hinder market competition, and keep prices high [18••]. Multiple ideas have arisen to gain control of the increasing drug prices, such as creating policies that prohibit pharmaceutical companies from reformulating a drug with no additional therapeutic benefit.

Table 2 Second-line and beyond drug regimens in multiple myeloma and associated costs [29]

Line of therapy	Regimen	Schedule	Cost (WAC) [29]	Cost per cycle	Annual cost		Patient responsibility
Second line	KPD [39, 40]	Carfilzomib: 20 mg/m^2 day 1, 2 (cycle 1), and 27 mg/m^2 days 8, 9, 15, 16 (and all subsequent doses) Pomalidomide: 4 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly #Alternative Dosing Carfilzomib: 20 mg/m^2 day 1 (cycle 1), 56 mg/m^2 days 8, 15 (and all subsequent dosing) Pomalidomide: 4 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Carfilzomib: WAC $49.65/mg Pomalidomide: $21,123	Carfilzomib: C1: $12,812 C2–12: $14,004 C13+: $9336 Pomalidomide: $21,123 Alternate carfilzomib: C1: $11,470 C2+: $14,598	Year 1: Traditional carfilzomib: $420,332 Alternate carfilzomib: $425,520	Year 2: Traditional carfilzomib: $365,508 Alternate carfilzomib: $428,652	Traditional carfilzomib: Year 1: Part B: $33,371 Part D: $50,695 Year 2 and beyond: Alternate carfilzomib: Year 1: Part B: $34,410 Part D: $50,695 Year 2 and beyond: Part B: $35,035 Part D: $50,695
	DVD* [41]	Daratumumab: days 1, 8, 15, 22 (cycles 1–2), days 1 and 15 (cycles 3–6), every 28 days (cycle 7+) Bortezomib: 1.3 mg/m^2 days 1, 8, 15, 22 Dexamethasone: 40 mg weekly	Darzalex Faspro: $9119 per 1800–30,000 mg/15-mL vial Bortezomib 3.5 mg: $75 per vial	Darzalex Faspro: C1-C2: $36,476 C3-6: $18,238 C7+: $9119 Bortezomib: $200	Year 1: $203,018	Year 2: $111,828	Year 1: Part B: $40,604 Year 2 and beyond: Part B: $22,366
	DKD* [42, 43]	Daratumumab: days 1, 8, 15, 22 (cycles 1–2), days 1 and 15 (cycles 3–6), every 28 days (cycle 7+) Carfilzomib: 20 mg/m^2 day 1, then 56 mg/m^2 days 8, 15 (and all subsequent doses) Dexamethasone: 40 mg weekly	Darzalex Faspro: $9119 per 1800–30,000 mg/15-mL vial Carfilzomib: WAC $49.65/mg	Darzalex Faspro: C1–C2: $36,476 C3–6: $18,238 C7+: $9119 Carfilzomib: C1: $3,475 C2+: $29,194	Year 1: $525,227 (12 cycles)	Year 2: $459,756	Year 1 Part B: $105,045 Year 2 and beyond Part B: $91,951
	DPD* [44]	Daratumumab: days 1, 8, 15, 22 (cycles 1–2), days 1 and 15 (cycles 3–6), every 28 days (cycle 7+) Pomalidomide: 4 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Darzalex Faspro: $9119 per 1800–30,000 mg/1-5 mL vial Pomalidomide: $21,123	Darzalex Faspro: C1–C2: $36,476 C3–6: $18,238 C7+: $9119 Pomalidomide: $21,123	Year 1: $454,094	Year 2: $362,904	Year 1: Part B: $40,124 Part D: $50,695 Year 2 and beyond: Part B: $21,886 Part D: $50,695
	IsaKD* [45]	Isatuximab: 10 mg/kg weekly cycle 1, then every other week thereafter Carfilzomib: 20 mg/m^2 on days 1, 2, then 56 mg/m^2 days 8, 9, 15, 16 (and all subsequent doses) Dexamethasone: 20 mg days 1, 2, 8, 9, 15, 16, 22, 23	Isatuximab: $7.35/mg Carfilzomib: WAC $49.65/mg	Isatuximab: C1: $23,520 C2+: $11,760 Carfilzomib: C1: $22,940 C2+: $29,196	$496,976		Part B: $99,395

Table 2 (continued)

Line of therapy	Regimen	Schedule	Cost (WAC) [29]	Cost per cycle	Annual cost		Patient responsibility
Second line	IRD* [38]	“”	Ixazomib: $12,240 Lenalidomide (generics): WAC $720/capsule	Ixazomib: $12,240 Lenalidomide: $15,120	$328,320		Part D: $65,664
	ERD*^ [46]	Elotuzumab: 10 mg/kg weekly cycles 1–2, then every other week thereafter Lenalidomide: 25 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Elotuzumab: WAC $2803 per 400 mg Lenalidomide (generics): WAC $720/capsule	Elotuzumab: C1–2: $22,424 C3+: $11,212 Lenalidomide: $15,120	$338,408		Part B: $31,394 Part D: $36,288
	DRD* [35]	“”	Darzalex Faspro: $9119 per 1800–30,000 mg/15-mL vial Lenalidomide (generics): WAC $720/capsule	Darzalex Faspro: C1–C2: $36,476 C3–6: $18,238 C7+: $9119 Lenalidomide: $15,120	Year 1: $382,058	Year 2: $290,868	Year 1: Part B: $40,124 Part D: $36,288 Year 2 and beyond: Part B: $21,886 Part D: $36,288
	KRD* [32, 33]	“”	Carfilzomib: WAC $49.65/mg Lenalidomide (generics): WAC $720/capsule	Traditional Carfilzomib: C1: $12,812 C2–12: $14,004 C13+: $9,336 Lenalidomide: $15,120 Alternate carfilzomib: C1: $11,470 C 2+: $14,598	Year 1: Traditional carfilzomib: $348,296 Alternate carfilzomib: $353,488	Year 2: Traditional carfilzomib: $293,472 Alternate carfilzomib: $356,616	Traditional carfilzomib: Year 1: Part B: $33,371 Part D: $36,288 Year 2 and beyond: Part B: $22,406 Part D: $36,288 Alternate carfilzomib: Year 1: Part B: $34,410 Part D: $36,288 Year 2 and beyond: Part B: $35,035 Part D: $36,288

Table 2 (continued)

Line of therapy	Regimen	Schedule	Cost (WAC) [29]	Cost per cycle	Annual cost	Patient responsibility
Third-line and beyond	IsaPD* [47]	Isatuximab: 10 mg/kg weekly cycle 1, then every other week thereafter Pomalidomide: 4 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Isatuximab: $7.35/mg Pomalidomide: $21,123	Isatuximab: C1: $23,520 C2+: $11,760 Pomalidomide: $21,123	$406,365	Part B: $30,576 Part D: $50,695
	PVD* [48]	Pomalidomide: 4 mg days 1–21 of 28 day cycle Bortezomib: 1.3 mg/m^2 days 1, 8, 15, 22 Dexamethasone: 40 mg weekly	Pomalidomide: $21,123 Bortezomib 3.5 mg: $75 per vial	Pomalidomide: $21,123 Bortezomib: $200	$255,876	Part B: $480 Part D: $50,695
	IPD [49]	Ixazomib: 4 mg days 1, 8, 15 Pomalidomide: 4 mg days 1–21 of 28 day cycles Dexamethasone: 40 mg weekly	Ixazomib: $12,240 Pomalidomide: $21,123	Ixazomib: $12,240 Pomalidomide: $21,123	$400,356	Part D: $80,071
	KD*[50]	Cycle 1: Carfilzomib: 20 mg/m^2 days 1, 2, then 56 mg/m^2 days 8, 9, 15, 16 (and all subsequent doses) Dexamethasone: 40 mg weekly	Carfilzomib: WAC $49.65/mg	Carfilzomib: C1: $22,940 C2+: $29,196	$344,096	Part B: $68,819
	CyBorD* [51]	Cyclophosphamide: 300 mg/m^2 days 1, 8, 15, 22 Bortezomib: 1.3 mg/m^2 days 1, 8, 15, 22 Dexamethasone: 40 mg weekly	Cyclophosphamide IV: $0.37 per mg Cyclophosphamide PO: (dispense 10×50 mg ($13.75 each) and 1×25 mg ($7.49 each)) $145 Bortezomib 3.5 mg: $75 per vial	Cyclophosphamide IV: $777 PO: $580 Bortezomib: $200	Using IV cyclophosphamide: $11,724 Using PO cyclophosphamide: $9360	Using IV cyclophosphamide: Part B: $2345 Using PO cyclophosphamide: Part B: $480 Part D: $1392
	SelVD* [52]	Selinexor: 100 mg weekly Bortezomib: 1.3 mg/m^2 weekly Dexamethasone: 40 mg weekly	Selinexor: $26,859 Bortezomib 3.5 mg: $75 per vial	Selinexor: $26,859 Bortezomib: $200	$324,708	Part B: $480 Part D: $64,462
	EPD^ [53]	Elotuzumab: 10 mg/kg weekly cycles 1–2, then every 4 weeks thereafter Pomalidomide: 4 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Elotuzumab: WAC $2,803 per 400 mg Pomalidomide: $21,123	Elotuzumab: C1–2: $22,424 C3+: $11,212 Pomalidomide: $21,123	$410,444	Part B: $31,394 Part D: $50,695
	PD* [54]	Pomalidomide 4 mg days 1–21 of 28 day cycle Dexamethasone: 40 mg weekly	Pomalidomide: $21,123	Pomalidomide: $21,123	$253,476	Part D: $50,695

Table 2 (continued)

Line of therapy	Regimen	Schedule	Cost (WAC) [29]	Cost per cycle	Annual cost	Patient responsibility
Fourth-line and beyond	Idecabtagene vicleucel [55]	LD chemo: Cyclophosphamide 300 mg/m^2×3 days Fludarabine 30 mg/m^2×3 days	Cyclophosphamide IV: $0.37 per mg Fludarabine: $2.18 per mg Idecabtagene vicleucel: $457,255	Conditioning regimen (IV): $930 Idecabtagene vicleucel: $457,255	$458,185	Part B: $91,637
	Ciltacabtagene vicleucel [56]	LD chemo: Cyclophosphamide 300 mg/m^2×3 days Fludarabine 30 mg/m^2×3 days	Cyclophosphamide IV: $0.37 per mg Fludarabine: $2.18 per mg	Conditioning Regimen (IV): $930 Ciltacabtagene vicleucel: $465,000	$465,930	Part B: $93,186
	Teclistamab-cqyv [57]	0.06 mg/kg day 1, 0.3 mg/kg day 4, 1.5 mg/kg day 7, then 1.5 mg/kg weekly thereafter	Teclistamab-cqyv: $1770 per 30 mg $9027 per 153 mg $59 per mg	C1: $39,648 C2+: $36,108 Drug cost (not including billed waste): C1: $30,019 C2+: $28,320	Including billed waste: $436,836 Not including billed waste: $341,539	Part B: Including billed waste: $87,367 Not including billed waste: $68,308
	Belantamab mafodotin-blmf (compassionate use only) [58]	2.5 mg/kg every 3 weeks	Belantamab: $88.26 per mg	$17,652 every 3 weeks	$300,084 (17 doses per year)	Part B: $60,017

*Category 1 NCCN v3.23; *WAC* wholesale acquisition cost, *IV* intravenous, *PO* oral

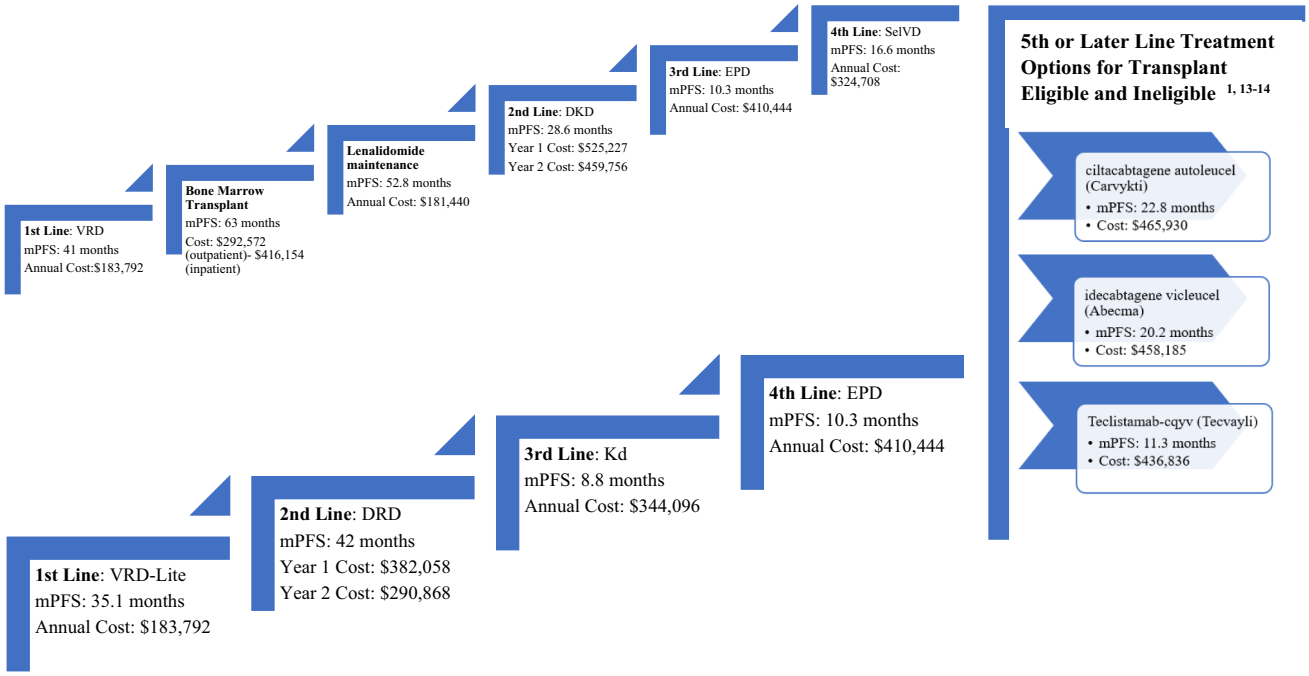

Fig. 1 Common treatment pathways for a transplant eligible [1•, 2•, 3•, 4•, 5••, 6, 7••, 8••] and non-transplant eligible/frail patient with multiple myeloma [1•, 9, 10•, 11•, 12••]

With novel policies or intellectual property patent reform, there would be an increase in generic options that allow the prices to come down, requiring all agents to decline in price. Another option includes value-based reimbursement, which would involve negotiation of the drug price after it is approved based on the value it brings to society and patients' lives [3•].

The IRA will cap OOP expenditures for Medicare patients at $2000 per beneficiary in 2025. While this is a tremendous step forward for patient care and reduction of financial toxicity, this will shift more cost share to the Medicare trust fund. Under the IRA, CMS will negotiate drug prices for the 10 highest gross spend Part D for implementation in 2026, 15 Part D drugs for 2027, and 15 drugs across Part B and Part D for 2028 [21••]. We have observed pay-for-delay strategies and patent thickets numerous times in the pharmaceutical industry even recently with lenalidomide, which offers another opportunity for the government to influence change from a policy level [22••]. Several key medications listed in Tables 1 and 2 will go generic in the next few years including pomalidomide in 2026, carfilzomib in 2027, ixazomib in 2028/2029, daratumumab IV in 2029, and isatuximab in 2032 [23•]. Given the significant use of these products in MM for Medicare beneficiaries, the government should consider investing in patents and manufacturing these therapies at a reasonable benchmarked price that keeps manufacturers incentivized to produce to prevent drug shortages and set a more affordable price for patients and Medicare.

Accelerated approval of agents in the oncology setting has faced recent scrutiny with withdrawal from the US market due to failure of confirmatory drug trials. Melphalan flufenamide was granted FDA accelerated approval in February 2021 and was withdrawn in November 2021; belantamab mafodotin-blmf is another agent granted FDA accelerated approval in April 2020 and subsequently withdrawn in November 2022 though remains in the market for compassionate use. In 2021, Medicare Part B spent $859,764 on melphalan flufenamide for a total of 51 claims and 41 patients and average spending per patient was $20,970 [24••]. In 2021, Medicare Part B spent $31,749,711 on belantamab mafodotin for a total of 1791 claims and 600 patients, and average spending per patient was $52,916 [24••]. The time is ripe for policy makers and the FDA to start considering costs and leverage the uncertainty price principle or "march-in rights" when granted accelerated approvals [25••].

From a patient perspective, the complexity and lack of transparency of costs are overwhelming. Pharmaceutical manufacturers are not allowed to provide co-pay coupons to federal healthcare programs, including Medicare Part D, as it violates the anti-kickback statutes [26••]. Medicare Part D patients could use co-pay coupons if they did not process the prescription through Medicare Part D, though manufacturers may be liable for violation of the anti-kickback statue [26••]. Medicare patients could obtain financial assistance through grant programs; however, grant funding may not be available when patients are in need and the amount of assistance provided varies. Grant funding typically requires proof of income

to determine if eligibility requirements are met. The Leukemia and Lymphoma Society sets their household income limit at 600% of the federal poverty level, which for a household of two requires household income to be below $118,320 [27••]. Navigating the grant process and patient assistance can be challenging and many healthcare providers do not have access to the same resources to support patients in navigating the process. Huntington et. al. surveyed 111 MM patients over a 3-month period using the COmprehensive Score for financial Toxicity (COST) assessment and found that 71% of patients had at least minor financial burden, 59% had higher financial burden than expected, 46% used savings to pay for treatments, 36% applied for financial assistance, and 21% of patients borrowed money to pay for medications [28••].

Once patients have relapsed numerous times and enter fourth line and beyond, there is less evidence-based guidance and increased ambiguity on what the next best therapy is. Figure 1 demonstrates how prices are compounded as patients progress and how later-line therapies are simply shadow priced to comparator therapies despite not having superior efficacy or survival benefit. While NCCN strives for clarity by creating evidence blocks, there is still room for improvement in cost transparency and cost-effectiveness. Given the lack of strong evidence and high costs, shared decision-making treatment discussions are of the utmost importance to balance efficacy, quality of life, and financial toxicity [28••].

Conclusion

Given the lack of clear-cut treatment recommendations for multiple myeloma in published guidelines and recognizing that patient and disease-specific considerations exist, treatment guidance for providers will continue to be a challenge. While new emerging drug therapies in multiple myeloma are exciting and changing the treatment paradigm, unfortunately, affordability is not on the near horizon and therapy costs may continue to significantly deplete the Medicare trust fund. There is significant opportunity for healthcare policy makers to step in and drive change to reduce healthcare costs for a financially vulnerable population and for US taxpayers. Only time will tell how impactful the Inflation Reduction Act and Medicare price negotiations have in reducing costs to patients and to the Medicare trust fund and its ability to provide stability and sustainability for the US healthcare system.

Declarations

Conflict of Interest Chelsee Jensen declares consulting work for Amgen regarding the current biosimilar landscape in October and December 2022. Nandita Khera declares honorarium from Incyte. Tyler Sandahl declares consulting work for Janssen regarding implementation of bispecific antibodies in January 2023. Sikander Ailawadhi declares consulting work for GSK, Sanofi, BMS, Takeda, Beigene, Janssen, Regeneron, Cellectar, and Pfizer. Dr. Ailawadhi also declares research funding to institution, Mayo Clinic, from GSK, BMS, Pharmacyclics, Amgen, Janssen, Cellectar, Abbvie, Ascentage, and Sanofi.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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