Current Hematologic Malignancy Reports (2022) 17:206–216
https://doi.org/10.1007/s11899-022-00669-1

HEALTH ECONOMICS (N KHERA, SECTION EDITOR)

Value in Myeloma Care: Myth or Reality

Evguenia Ouchveridze[1] · Katherine Berger[2] · Ghulam Rehman Mohyuddin[3]

Accepted: 11 July 2022 / Published online: 30 August 2022

Abstract

Purpose of Review Despite tremendous advances in multiple myeloma (MM) care, the disease maintains considerable morbidity and requires long-term treatment associated with significant financial toxicity to patients and high costs to society. In this review, we explore why — despite treatment advances — value in MM treatment is largely a myth, then explain some ways the myth might become a reality.

Recent Findings We discuss how value-based care in MM should include patient-centered outcomes such as financial toxicity and quality of life, which are heavily impacted by cost of drugs and the indefinite duration of therapy that is standard in MM treatment. We propose multiple paths to work toward reducing cost and augmenting value of care for patients with MM, including improving access to generic drugs, increasing federal funding for clinical trials, designing more patient-centric clinical trials, and exploring the utilization of minimal residual disease (MRD)-driven treatment de-escalation, among others.

Summary We remain optimistic that despite the challenges, we can work toward making progress in the realm of value-based care for patients with MM and make it a reality.

Keywords Multiple myeloma · Value · Cost · Financial toxicity · Patient centered · quality of life · Minimally residual disease (MRD)

Introduction

The treatment of multiple myeloma (MM) has dramatically advanced over the last decades with overall survival projected to exceed 10 years for many patients diagnosed today [1]. Indeed, these advances have led to a fundamental debate about whether MM is a chronic disease that may be controlled, or whether it may in fact be cured [2]. MM may thus differ from other hematologic malignancies where there is an inherent expectation of cure, such as in diffuse large B cell lymphoma (DLBCL) or Hodgkin lymphoma. MM also differs from other blood diseases such as acute myeloid leukemia, where life expectancy is much shorter. Similarities may be drawn between MM and chronic lymphocytic leukemia or chronic myeloid leukemia where current treatment paradigms generally also favor treatment as a chronic disease with long-term treatments.

As MM has largely been treated as a chronic disease, with medications given for prolonged periods of time, treatment has become increasingly expensive and has led to pervasive financial toxicity [3]. Medications for other cancers such as DLBCL may be expensive, but they are usually not given for years at a time. In MM, by contrast, patients stay on combination therapy with multiple drugs for many years.

As such, we see value-based care in MM in the current infrastructure as a myth, despite the incredible achievements seen in this disease. That said, we retain optimism that value-based care could become a reality. Herein, we will discuss the current landscape in MM from the standpoint of value-based care. We will discuss areas where improvements can be made, to not only decrease cost from a societal standpoint and advocate for legislative changes, but also to refocus clinical trials to use more patient-centered outcomes, and generally to shift the focus of therapy to limited duration

This article is part of the Topical Collection on *Health Economics*

✉ Evguenia Ouchveridze
jenny.ouchveridze@gmail.com

[1] Department of Hematological Malignancies and Cellular Therapeutics, Suite 210, Kansas University Medical Center, 2330 Shawnee Mission Parkway, Westwood, KS 66205, USA

[2] University of Hartford, West Hartford, CT, USA

[3] Division of Hematology and Hematological Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

treatments, de-escalated as appropriate, with favorable use of minimal residual disease (MRD)-guided treatment decisions as applicable.

The Improvement of Outcomes in MM

The treatment of MM has undergone tremendous evolution over the past 20 years, with multiple medications across several classes of drugs, such as proteasome inhibitors, immunomodulatory drugs, and anti-CD38 antibodies, as well as use of autologous stem cell transplant, all cumulatively leading to prolonged survival [4]. Figure 1 highlights the timeline of drug approval in MM. To contrast, the treatment in 1995 for MM was prednisone and melphalan, with 5-year overall survival at around 29%, and most patients dying within 2–3 years of diagnosis [5].

The Cost Factor

The improvement in survival rates with each new approval since 1995 has come at a significant cost [6]. In the current infrastructure, each newly approved drug is priced quite high, regardless of the incremental improvement it may (or may not) make for patients and their outcomes [7]. Table 1 lists the price of commonly used MM drugs. Unfortunately, for many of these options, generic drugs are either not available or their availability is hindered by multiple factors that affect practical access to the drug. Ultimately, this leads to unsustainably high costs to society for these medications [10].

As an example, although MM remains a fairly rare cancer with only 34,470 new cases diagnosed in the US population [11], the continuous therapy combined with multidrug combinations has made brand name lenalidomide (Revlimid) the second most costly drug expense for Medicare Part D [12].

Why are the Costs so High?

The high price of cancer medications is a complex multifactorial issue that cannot be done justice within the scope of this review. It is true that the price of drug development is high — a recent independent estimate claimed that bringing a drug to market cost an average of $985.3 million [13], and another independent estimate puts the cost at $648 million [14].

Another issue that contributes to high drug costs is the virtual monopoly of each drug when it is brought to the market, as the existence of multiple drugs for the same indication does not create downward pressure on drug prices. As an example, although isatuximab has a lower sticker price than daratumumab, its approval has not led to a substantial decrease in the cost of daratumumab, despite both being anti CD38 monoclonal antibodies with the same receptor target [15].

Furthermore, the seriousness of a diagnosis of a cancer such as MM makes one willing to accept whatever price is asked for by the drug developer, and this vulnerability indeed is ripe for exploitation by industry — especially in the USA, where insurance companies and government agencies pay for most of the cost of the drug, rather than the individual patient [10]. In the USA, there are laws that prevent Medicare from negotiating drug prices with the industry. Although there have been recent political efforts to enact change and allow for negotiation, these changes have been met with roadblocks, and prices remain high [16].

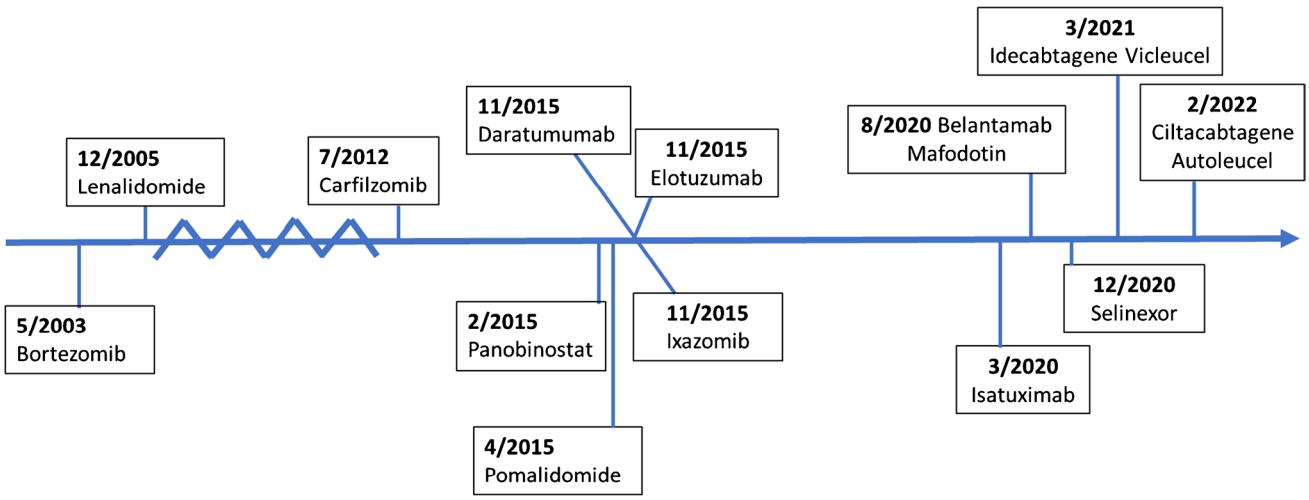

Fig. 1 Drug approval timeline in MM in the past 20 years

Table 1 Current prices of drugs that have gained approval for MM in the last 20 years

Drug	Initial approval	Route	Dose unit	Quantity	Cost of oral medications 2022		Cost per injection		
					Per tablet/capsule	Per quantity specified[1]	2022	2019	2017
Ciltacabtagene autoleucel	Feb 2022	IV	1 dose	Single injection			$489,655		
Idecabtagene vicleucel	Mar 2021	IV	1 dose	Single injection			$441,743		
Belantamab mafodotin	Aug 2020	IV	100 mg	Single injection			$9,077.08		
Selinexor	Dec 2020	Oral	20 mg	8 tablets	$3038.83	$24,310.63			
		Oral	20 mg	24 tablets	$1082.84	$25,988.06			
Isatuximab	Mar 2020	IV	100 mg/5 mL	Single injection			$746.58		
		IV	450 mg/25 mL	Single injection			$3694.89		
Elotuzumab	Nov 2015	IV	300 mg	Single injection			$2147.79	$1947.30	$1863.00
Ixazomib	Nov 2015	Oral	2.3 mg	3 capsules	$3826.96	$11,480.88			
Daratumumab	Nov 2015	IV/SQ	100 mg/5 mL	Single injection			$655.83	$537.51	$481.05
		IV	400 mg/20 mL	Single injection			$2594.82	$2150.04	$1924.20
Panobinostat	Feb 2015	Oral	10 mg	6 capsules	$2473.06	$14,838.38			
Pomalidomide	Apr 2015	Oral	1 mg	21 capsules	$999.17	$20,982.61			
Carfilzomib	Jul 2012	IV	30 mg	Single injection			$1447.52	$1117.44	$966.12
		IV	60 mg	Single injection			$2,885.54	$2,234.88	$1,932.24
Lenalidomide	Dec 2005	Oral	25 mg	21 capsules	$877.84	$18,434.61			
		Oral	10 mg	28 capsules	$877.72	$24,576.29			
Bortezomib	May 2003	SQ	3.5 mg	Single injection			$213.50	$881.69	$1,618.40

Total cost for the number of pills or capsules that are commonly dispensed, as specified under "quantity" Source: Drugs.com/price-guide, accessed 5/17/22 [8] https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2017ASPFiles, accessed 7/9/22 [9]

Defining and Assessing Value in MM

Traditionally, the endpoints that matter most to patients are living longer (overall survival) and living better (quality of life) [17]. It is therefore critical that in MM, health-related quality of life (HRQOL) outcomes be transparently reported and longitudinally measured. HRQOL is very rarely a primary endpoint of a randomized trial [18] and when reported is often reported incompletely and in a heterogeneous way [19]. As such, information on whether treatment truly helps patients' HRQOL (especially for treating smaller and smaller amounts of disease in the relapsed/refractory setting) remains elusive, and becomes of more concern, as increasingly smaller amounts of disease may be detected and treated [20]. Transparent, longitudinal reporting of quality of life is a step forward in helping regulators ascertain value of care. As a positive example, it has been shown that after use of novel chimeric antigen receptor therapy (CAR-T), there was an improvement in pain, fatigue, overall QOL, and physical functioning by month 2 post CAR-T, an effect which was sustained through months 15–18 after therapy [21].

Furthermore, in order to have transparent discussions and determinations on value in MM, assessments of whether newer treatments are improving overall survival need to be made. Simply moving treatments to the newly diagnosed setting and "combining" therapies rather than "sequencing" them may not be the best use of resources [22], unless the cure fraction is substantially increased. Unfortunately, improvement in surrogate outcomes alone often drives a push towards increased utilization of therapies, and although this may be justified as a patient-facing approach, it may lead to increased costs to society without a clear meaningful benefit to patients. An example of this is the incorporation of quadruplet therapy in newly diagnosed MM on the basis

of improvement in response rates or measurable residual disease alone, rather than waiting for longer term data on outcomes such as overall survival or HRQOL [23].

A model was proposed by Dr. Porter for assessing outcome measures in clinical scenarios [24]. The model is a hierarchical system based on the premise that multiple outcomes collectively define success of a treatment, with the outcomes of highest importance at the top, and the subsequent tiers are contingent on the success of the higher tiers [24]. A major limitation of this model in the context of MM patients is that individual patients hold different aspects of their care at differing levels of importance. As such, in the context of MM, this model would need to be fully customizable to the individual, as the value of care is seen differently in a younger, newly diagnosed individual as compared to a patient who has been exposed to a couple of years of therapy, versus a newly diagnosed elderly individual [25].

Financial Toxicity—Pervasive Yet Hidden

Another example of how MM treatment may lack adequate value, even to an individual patient, is the financial toxicity it imposes. This metric (financial toxicity) is under-represented in studies on MM [3]. Financial toxicity is inherently a heterogeneous measure and includes a combination of direct and indirect costs. *Direct costs* are payments made in direct relation to the medical care, such as co-payments, charges for medications, or doctor's visits, whereas *indirect costs* refer to the loss of work productivity, salary, and time related to the disease, its treatment and side effects (including time missed from work for infusions and other treatments) ultimately leading to a loss of income for the patient and possibly for a caregiver as well [26].

There is no standardized tool for the assessment of financial toxicity, however, and each study that assesses financial toxicity may utilize different question sets. This leads to a lack of a coordinated ability to assess the financial toxicity that patients may experience with the treatment of MM [3].

A recently published systematic review showed there is significant prevalence of financial toxicity in hematologic malignancies, irrespective of country or payor system. As was noted by that systematic review, only half of current studies on financial toxicity use a standardized assessment tool [3]. A pilot study conducted by Huntington et al., in 2015, used the COST questionnaire and surveyed 111 patients with MM overall a 3-month period. Of the 100 individuals who responded to the survey request, 59% of individuals in the study had higher financial burden than expected, and 71% had at least minor financial burden. Also, 46% used savings, 36% applied for financial assistance, and 21% borrowed money to pay for medications [27]. In order to understand this problem and rectify it, future studies must report this an outcome in a standardized fashion. Studies aimed at alleviating this problem are desperately needed.

Does the Landscape of Trial Design Optimize Value?

The relative lack of patient-centered strategic trials is another aspect requiring further exploration. There is a growing divide between the incentives that drive drug companies to develop trials and promote a drug on the one hand and patient-centered endpoints on the other. The chosen endpoints and prespecified subgroup analyses are generally aiming toward obtaining drug approval or a novel indication in an expedited fashion [28, 29].

As an example in the MM sphere, multiple trials have been conducted where the intervention arm and the control arms have differing number of active anti-myeloma drugs—three versus two drugs—in a clinical context where a three drug anti-myeloma regimen is the defined standard of care, already known to be superior to a two-drug regimen [30]. As such, it is known that multiple three drug regimens are efficacious in the relapsed setting but not known which one is more efficacious than the others; thus, the choice of which one to use largely depends on individual patient factors rather than the known superiority of one regime over another [31].

The improvements to MM survival render the use of overall survival a difficult endpoint in certain situations; nevertheless, it remains the primary goal of therapy [18]. Although it would be reasonable to use PFS as an endpoint in a front line setting where the anticipated survival is measured in many years, in a heavily pre-treated population where life expectancy is relatively short and survival data could be more easily obtainable, the outcome of overall survival is a much more relevant and patient-centered endpoint. Nevertheless, even in settings where overall survival is a valid and feasible endpoint, progression-free survival is often favored as a study endpoint. As an example, for maintenance therapy after CAR-T in heavily relapsed patients (the current post CART-T standard of care is observation without additional therapy until progression), extra therapy and inconvenience could be justified if it truly makes patients live longer. This benefit should not take too long to show. Nevertheless, a recent trial of belantamab as maintenance after CAR-T used progression-free survival as the primary endpoint (NCT05117008). It is likely that maintenance therapy after CAR-T may be adopted in the near future, denying patients a treatment break and contributing to increased costs of cancer care without a clear survival or HRQOL benefit for patients.

How can Costs be Brought Down and the "Value of Care" Increased?

To improve value in MM care requires numerous initiatives which we will highlight here. We discuss broad examples

that can be applicable to all cancer drugs, as well as specific examples within the MM trial design landscape.

Value-Based Pricing

Although a highly attractive concept, value-based pricing runs into a fundamental issue around how the definition of "value" in MM care is defined. What is important to patients and their families is different than what is important to another patient at a different stage in life, a company trying to obtain a drug approval, or to an insurance company or even to society at large.

Other than the USA, most countries do have agencies (in addition to those that provide regulatory approval) that determine the value of a drug [32]. Although there is no singular definition of what the value of a drug is, and various societies may indeed define this differently, the absence of any such mechanism in the USA leads to an unopposed monopoly of industry dictating prices. It is thus critical that a robust, independent agency that defines value of drugs be incorporated, similar to what exists in other countries. We must also enable Centers for Medicare & Medicaid Services to negotiate costs directly, enacting a system similar to those in Europe and Canada. However, we do recognize that this idea requires legislative change and is impossible without robust patient-driven grassroots movements [33].

Decreasing Barriers to Generic Drugs

In order to decrease costs for MM drugs, it is absolutely essential that approval of generics and biosimilars become significantly easier. In the current landscape, major pharmaceutical companies engage in strategies and negotiations that delay the launch of generic drug. Although generic lenalidomide has been available globally for many years, in the USA, several strategies were used that substantially delayed its launch, such as limiting generic competitors' access to samples of the drug, making deals with generic companies for a very limited market access, and maintaining exclusivity of the company's REMS program [34]. There must be legislative reform that prevents such tactics and allows rapid access of multiple generic products to the market.

Evaluating Decreased Duration and Dose of Treatment

We must consider duration of treatment if we are to consider cost-effective care. We have the example of the MAIA trial, where daratumumab, lenalidomide, and dexamethasone were given as a continuous regimen in the frontline transplant ineligible setting [35]. It is not surprising that numerically, the duration of remissions achieved with this regimen is longer than with other less intense, more "finite" regimens [36]. However, considering the cost of daratumumab, it could be informative to study a limited duration use of the drug, especially because continuous administration may not be needed, based on lessons learned from another daratumumab trial, where continuous daratumumab maintenance gave no additional benefit to those who had received it during induction [37]. However, such a trial design (although currently in early stages of development through the Southwest Cooperative Group in a subset of frail patients) may not be as financially advantageous for industry.

Furthermore, companies may not be incentivized to find lower effective doses of their drugs or to consider "intermittent" dosing strategies. This must be a question that cooperative groups and investigator-initiated trials should strive to answer, as in the trial evaluating every-other-day dosing of pomalidomide (NCT03520985). There is no shortage of such concepts, from reduced doses to limited duration treatment and beyond, which can be explored in MM, given the multiplicity of drugs and regimens approved, as well as surrogate endpoints that can provide quick measures of activity in a reasonable timeframe.

Can using MRD Negativity to Adapt and De-escalate Treatment Bring Value?

A major consideration in MM treatment, as well as study design, is minimally residual disease (MRD)-driven treatment decision-making. Achievement of MRD negativity has emerged as an investigative endpoint in most recent years and more recently has been shown to be strongly prognostic for progression-free survival [38]. The techniques for assessing MRD, including NGS and next-generation flow (NGF), as well as circulating tumor cells and mass spectrometry, are under ongoing study. Techniques have not yet been standardized across trials, although recent attempts have been made to do so [39].

Table 2 highlights ongoing trials that are using MRD status to guide further decision-making. The MASTER trial as a proof of concept has shown that intensive up-front therapy followed by measurable residual disease–guided observation (as opposed to continuous maintenance therapy) is theoretically feasible [40]. Further examples on the use of measurable residual disease–guided management include the MIDAS and MASTER-2 trial. Both these trials (listed in Table 2) evaluate whether autologous stem cell transplant can be omitted for those patients who achieve deep responses to initial induction therapy. Nevertheless, these trials do utilize expensive induction and consolidation regimens, and the use of autologous stem cell transplantation is actually a rather more affordable measure in low resource settings compared to these therapies. However, the omission of continuous lenalidomide maintenance in those that achieve measurable residual disease negativity after 2 years of maintenance,

Table 2 Ongoing MRD trials

Title	Study name	Intervention	NCT	Status	Phase	Enrollment goal	Study start	Update expected	Primary endpoint
Short course daratumumab in minimal residual disease (MRD) positive myeloma patients after induction therapy with/without consolidative high dose chemotherapy/autologous stem cell support	N/A	C1/C2-dara weekly for 8 weeks; C3-6-dara q2 wks for 16 weeks; Len 5-15 d21-28/28d cycles	NCT03490344	Recruiting	2	25	May 2018	Oct 2023	MRD negativity at completion of dara therapy
A Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Participants With Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant (AURIGA)	AURIGA	C1/C2-dara weekly, C3-6-dara q2 wks, C7+ dara q4wks; Len 10mg continuous.	NCT03901963	Recruiting	3	214	Apr 2019	Oct 2023	MRD negative at 12 months
Phase 2 study with minimal residual disease (MRD)-driven adaptive strategy in treatment for newly diagnosed multiple myeloma (MM) with upfront daratumumab-based therapy	N/A	C1/C2- dara weekly, C3-6 q2wks, C7-C9 q4 wks, C10+ q8wk maintenance. Len induction 25 d1-21/28, consolidation same, maintenance 10mg daily d1-21/28	NCT04140162	Recruiting	2	50	Oct 2020	Oct 2024	MRD negative after induction, and after consolidation
Post-autologous transplant maintenance with isatuximab and lenalidomide in minimal residual disease positive multiple myeloma (HEME-18)	HEME-18	Isatuximab C1 D1,8,15,22; C2/3 D1, D15; C4+ D1; Len 15 D1-28 C4+ continuous.	NCT05344833	Not yet recruiting	2	50	May 2022	Dec 2030	MRD negative CR at one year
Pre-emptive Daratumumab Therapy of Minimal Residual Disease Reappearance or Biochemical Relapse in Multiple Myeloma (PREDATOR)	PREDATOR	Arm A-dara; Arm B-observation	NCT03697655	Recruiting	2	274	Dec 2018	Jul 2024	EFS

Table 2 (continued)

Title	Study name	Intervention	NCT	Status	Phase	Enrollment goal	Study start	Update expected	Primary endpoint
Belantamab mafodotin and lenalidomide for the treatment of multiple myeloma in patients with minimal residual disease positive after stem cell transplant	N/A	Belantamab D1, Len D1-28. Repeat q8 wks for 6 cycles	NCT04876248	Not yet recruiting	2	20	Jul 2022	Jul 2024	MRD pos to negative conversion rate
Minimal Residual Disease Response-adapted Deferral of Transplant in Dysproteinemia (MILESTONE)	MILESTONE	Dara-RVD x 6 cycles, and if negative defer autologous SCT. If positive, autologous SCT and monitor for MRD negativity post-transplant as 2ndary outcome	NCT04991103	Recruiting	2	20	Sep 2021	Jan 2025	MRD negativity
Minimal residual disease guided maintenance therapy with belantamab mafodotin and lenalidomide after autologous hematopoietic cell transplantation in patients with newly diagnosed multiple myeloma	N/A	Maintenance with belantamab q8 weeks initially x6 cycles then q12 weeks for cycle 7 onward. Other arm is lenalidomide maintenance 10/d continuous	NCT05091372	Not yet recruiting	2	94	Apr 2022	Mar 2025	MRD pos to negative conversion rate
Study to assess for measurable residual disease (MRD) in multiple myeloma patients	MRD2STOP	After at least 1 yr of maintenance tx, identification of MRD negativity on PET, flow cytometry and NGS-> if yes, will discontinue maintenance therapy	NCT04108624	Recruiting	N/A	56	Oct 2019	Dec 2022	MRD neg to pos after d/c maintenance therapy; PFS, OS
MInimal Residual Disease Adapted Strategy (MIDAS)	MIDAS	MRD Standard-risk post induction MRD <10-5,(1:1 Randomization):Arm A: 6 additional cycles of Isa-KRD Arm B: ASCT followed by 2 cycles of Isa-KRD MRD High-risk (post induction MRD >10-5) (1:1 Randomization) Arm C: ASCT followed by 2 cycles of Isa-KRD Arm D: tandem ASCT	NCT04934475	Recruiting	3	716	Dec-21	Dec-24	Neg MRD rate

Table 2 (continued)

Title	Study name	Intervention	NCT	Status	Phase	Enrollment goal	Study start	Update expected	Primary endpoint
Sequential Therapy in Multiple Myeloma Guided by MRD Assessments (MASTER-2)	MASTER-2	Arm A: 3 cycles of Dara-VRd intensification followed by 13 cycles of Dara-R maintenance in MRD negative patients; Arm B: AHCT intensification followed by 13 cycles of Dara-R maintenance in MRD negative patients; Arm C: AHCT intensification, 3 cycles of Dara-Tec consolidation and 13 cycles of Dara-Tec maintenance in MRD positive patients; Arm D: AHCT intensification, 3 cycles of Dara-R consolidation and 13 cycles of Dara-R maintenance in MRD positive patients	NCT05231629	Not yet recruiting	2	300	Aug-22	Apr-26	Depth of response, and MRD negativity

as is being studied in the DRAMMATIC trial, represents a potential cost-saving measure given the current cost of lenalidomide. Although MRD-driven decision-making can offer opportunities for individualizing treatment, and may conceivably reduce costs, they may bring in costs of their own and as such are not yet widely applicable outside of the research setting. We and others envision a future where high-intensity therapy is given for a short period of time, with sustained treatment-free intervals following.

We Must Prove Newer Therapies are Better than Older Therapies Before Adopting Newer Therapies

Although the allure of using newer therapies is ever-present, there must be efforts to encourage direct comparisons of newer agents to older existing therapies before their widespread implementation. As an example, melphalan flufenamide (melflufen) represented a slight modification to a drug that had been present since over 60 years (melphalan) [41]. A peptide conjugate was added with preclinical data demonstrating increased activity over the original compound [41]. Melflufen was granted conditional approval based on a single-arm trial, only for this approval to be revoked after the drug led to a numerically larger number of deaths in the confirmatory randomized trial [42]. As older agents such as lenalidomide become generic, and newer medications with similar mechanisms of action (such as iberdomide) enter the market, we must be responsible in asking for robust data before automatically replacing the old with the new. Nevertheless, in at least one randomized trial, iberdomide maintenance is provided to multiple arms of the study, long term, without any direct comparison to lenalidomide (NCT04934475). Another example is the effort of a CAR-T product to overtake autologous transplantation without a head-to-head comparison in a population not "intended" for early transplant, despite patients enrolled in this trial often being fit enough to undergo transplant (NCT04923893). As long as the industry dictates funding for clinical trials, the landscape is likely to continue to prioritize "novelty" over value, and treatments will continue to get more expensive.

Increased Funding at the Federal Level for Clinical Trials

Ultimately, an important way to improve value in MM, and indeed for other cancers, is to vastly increase funding for clinical trial research. The current infrastructure for clinical trials is largely dictated by industry and may not be designed to maximize value [43]. As previously stated, there are many approved three drug regimens, but no way to sequence them; furthermore, there is no incentive to study sequencing therapies rather than combining them. Increased funding for clinical trials in MM will allow independent trials and agencies to design cost-effective strategies that truly seek the answer whether we can get the same or better outcomes by doing less therapy. Ultimately, this will require legislative change, lobbying from important stakeholders, and sustained, concerted effort from all involved.

The Advocacy of Physicians for Cost Reduction

In the current landscape where conflicts of interest are rife, physicians may not feel comfortable or feel it is in the best interest of their career growth to advocate for cost reduction [44, 45]. As a result, talk about cost of therapies, or advocacy for cost reduction, is often a very small part of the agenda at medical conferences [46], nor, in our opinion, is it a significant aim of major cancer societies. Commonly, physicians do not feel well equipped to discuss cost and financial toxicity with patients [47]. Nevertheless, to increase value in MM care, physician leaders must be part of these conversations and publicly advocate for change [48].

Shared Decision-Making

In the absence of adequate good quality data helping to guide the sequencing of therapies [22], high-level discussions with patients and shared decision-making hold an even greater importance. This includes not only efficacy discussion but also various quality of life measures, as well as costs and potential financial toxicity to the patient, all of which would have varying degrees of importance for each individual [47].

Conclusion

We have highlighted the ways in which value in MM care is, at present, largely a myth. We argue that these current trends are unsustainable, despite the tremendous improvements in outcomes. While appreciating the tremendous gains we have made, and lauding the efforts of industry, we propose various initiatives here that can collectively bring down the cost of therapy, make it sustainable from a cost and HRQOL standpoint, and bring more overall value to MM care. We recognize that these efforts are not easy and require concerted efforts and lobbying from all involved stakeholders, as well as legislative reforms.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11899-022-00669-1.

Declarations

Conflict of Interest The authors declare no competing interests.

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.

References

1. Joseph NS, Kaufman JL, Dhodapkar MV, Hofmeister CC, Almaula DK, Heffner LT, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. J Clin Oncol. 2020;38(17):1928–37.
2. Cavallo J Defining cure in multiple myeloma: a conversation with S. Vincent Rajkumar. 2021. Available from: https://ascopost.com/issues/july-10-2021/defining-cure-in-multiple-myeloma/. Accessed 17 May 2022.
3. Ouchveridze E, Banerjee R, Desai A, Aziz M, Lee-Smith W, Mian H, et al. Financial toxicity in hematological malignancies: a systematic review. Blood Cancer J. 2022;12(4):74.
4. Thorsteinsdottir S, Dickman PW, Landgren O, Blimark C, Hultcrantz M, Turesson I, et al. Dramatically improved survival in multiple myeloma patients in the recent decade: results from a Swedish population-based study. Haematologica. 2018;103(9):e412–e5.
5. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111(5):2521–6.
6. Bhattacharya K, Bentley JP, Ramachandran S, Chang Y, Banahan BF 3rd, Shah R, et al. Phase-specific and lifetime costs of multiple myeloma among older adults in the US. JAMA Netw Open. 2021;4(7):e2116357.
7. Vincent RS. The high cost of prescription drugs: causes and solutions. Blood Cancer J. 2020;10(6):71.
8. Prices of Drugs from drugs.com [Available from: https://www.drugs.com/price-guide/.
9. Medicare Part B Drug and Biological Average Sales Price: 2017 ASP Drug Pricing Files. 2017. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice. Accessed 9 July 2022.
10. Rajkumar SV. Value and cost of myeloma therapy. Am Soc Clin Oncol Educ Book. 2018;38:662–6.
11. SEER. SEER Cancer Stat Facts [Available from: https://seer.cancer.gov/statfacts/html/mulmy.html.
12. Dusetzina SB. Your money or your life — the high cost of cancer drugs under Medicare Part D. New England JMed 2022.
13. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA. 2020;323(9):844–53.
14. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med. 2017;177(11):1569–75.
15. CMS Drug Pricing. Available from: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files.
16. What's the latest on medicare drug price negotiations? Available from: https://www.kff.org/medicare/issue-brief/whats-the-latest-on-medicare-drug-price-negotiations/.
17. Gyawali B, Hey SP, Kesselheim AS. Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs. E Clin Med. 2020;21:100332.
18. Mohyuddin GR, Koehn K, Abdallah AO, Sborov W, Rajkumar D, Kumar SV, Mc Clune B, et al. Use of endpoints in multiple myeloma randomized controlled trials over the last 15 years: a systematic review. Am J Hematol. 2021;96(6):690–7.
19. Chakraborty R, Cannella L, Cottone F, Efficace F. Quality of patient-reported outcome reporting in randomised controlled trials of haematological malignancies according to international quality standards: a systematic review. Lancet Haematol. 2020;7(12):e892–901.
20. Anderson KC, Auclair D, Adam SJ, Agarwal A, Anderson M, Avet-Loiseau H, et al. Minimal residual disease in myeloma: application for clinical care and new drug registration. Clin Cancer Res. 2021.
21. Delforge M, Shah N, Miguel JSF, Braverman J, Dhanda DS, Shi L, et al. Health-related quality of life with idecabtagene vicleucel in relapsed and refractory multiple myeloma. Blood Adv. 2022;6(4):1309–18.
22. Mohyuddin GR, Koehn K, Abdallah AO, Goodman AM, Prasad V. Reporting of postprotocol therapies and attrition in multiple myeloma randomized clinical trials: a systematic review. JAMA Netw Open. 2021;4(4):e218084.
23. Mohyuddin GR, Mian H. Daratumumab in newly diagnosed MM - incorporating lessons learnt from CASSIOPEIA, MAIA and beyond. Nat Rev Clin Oncol. 2022;19(1):3–4.
24. Porter ME. What is value in health care? N Engl J Med. 2010;363(26):2477–81.
25. Oerlemans S, Bennink MC, Levin MD, Broijl A, Van der Klift M, Van Deursen J, et al. Development of a patient centered outcome set for patients with multiple myeloma to be used in clinical practice. Hemasphere. 2020;4(3):e366.
26. Witte J, Mehlis K, Surmann B, Lingnau R, Damm O, Greiner W, et al. Methods for measuring financial toxicity after cancer diagnosis and treatment: a systematic review and its implications. Ann Oncol. 2019;30(7):1061–70.
27. Huntington SF, Weiss BM, Vogl DT, Cohen AD, Garfall AL, Mangan PA, et al. Financial toxicity in insured patients with multiple myeloma: a cross-sectional pilot study. Lancet Haematol. 2015;2(10):e408–16.
28. Wesson W, Galate VL, Sborov DW, McClune B, Goodman AM, Gyawali B, et al. Characteristics of clinical trials for haematological malignancies from 2015 to 2020: a systematic review. Eur J Cancer. 2022;167:152–60.
29. Moreau P, Rajkumar SV. Multiple myeloma--translation of trial results into reality. Lancet. 2016;388(10040):111–3.
30. Mohyuddin GR, Koehn K, Sborov D, McClune B, Abdallah AO, Goodman AM, et al. Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review. Lancet Haematol. 2021;8(4):e299–304.
31. Unprecedented outcomes of Isatuximab [press release].
32. Antonanzas F, Terkola R, Postma M. The value of medicines: a crucial but vague concept. Pharmacoeconomics. 2016;34(12):1227–39.
33. Tefferi A, Kantarjian H, Rajkumar SV, Baker LH, Abkowitz JL, Adamson JW, et al. In support of a patient-driven initiative and petition to lower the high price of cancer drugs. Mayo Clin Proc. 2015;90(8):996–1000.
34. How a drugmaker gamed the system to keep generic competition away.
35. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019;380(22):2104–15.
36. Kapoor P, Rajkumar SV. MAIA under the microscope - bringing trial design into focus. Nat Rev Clin Oncol. 2019;16(6):339–40.
37. Moreau P, Sonneveld P, Investigators ftCS. Daratumumab (DARA) maintenance or observation (OBS) after treatment with bortezomib, thalidomide and dexamethasone (VTd) with or without DARA and autologous stem cell transplant (ASCT) in patients (pts) with newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 2. J Clin Oncol. 2021;39(15_suppl):8004.

38. Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv. 2020;4(23):5988–99.
39. Costa LJ, Derman BA, Bal S, Sidana S, Chhabra S, Silbermann R, et al. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. Leukemia. 2021;35(1):18–30.
40. Costa LJ, Chhabra S, Medvedova E, Dholaria BR, Schmidt TM, Godby KN, et al. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. J Clin Oncol 2021 JCO2101935.
41. Ray A, Ravillah D, Das DS, Song Y, Nordstrom E, Gullbo J, et al. A novel alkylating agent Melflufen induces irreversible DNA damage and cytotoxicity in multiple myeloma cells. Br J Haematol. 2016;174(3):397–409.
42. Olivier T, Prasad V. The approval and withdrawal of melphalan flufenamide (melflufen): Implications for the state of the FDA. Transl Oncol. 2022;18:101374.
43. Ehrhardt S, Appel LJ, Meinert CL. Trends in National Institutes of Health funding for clinical trials registered in ClinicalTrials.gov. JAMA. 2015;314(23):2566–7.
44. Abola MV, Prasad V. Characteristics and conflicts of public speakers at Meetings of the Oncologic Drugs Advisory Committee to the US Food and Drug Administration. JAMA Intern Med. 2016;176(3):389–91.
45. Wayant C, Turner E, Meyer C, Sinnett P, Vassar M. Financial conflicts of interest among oncologist authors of reports of clinical drug trials. JAMA Oncol. 2018;4(10):1426–8.
46. Mishra S. Do medical conferences have a role to play? Sharpen the saw. Indian Heart J. 2016;68(2):111–3.
47. Fischer KA, Walling A, Wenger N, Glaspy J. Cost health literacy as a physician skill-set: the relationship between oncologist reported knowledge and engagement with patients on financial toxicity. Support Care Cancer. 2020;28(12):5709–15.
48. Tao DL, Boothby A, McLouth J, Prasad V. Financial conflicts of interest among hematologist-oncologists on Twitter. JAMA Intern Med. 2017;177(3):425–7.