Value-Based Paradigms in Multiple Myeloma: Pharmacoeconomic Analysis of Novel Therapies

Introduction

Over the past 2 decades, the standard of care for multiple myeloma (MM) has shifted with the introduction of novel, targeted agents such as bortezomib, lenalidomide, and thalidomide.1 There is no doubt that these therapies have led to better clinical outcomes, as documented in an analysis by Kumar and colleagues of 2981 patients with newly diagnosed MM seen at their clinic over a 36-year period, from the start of 1971 to the end of 2006.2 These investigators reported that the subset of patients diagnosed from 1996 to 2006—the era of novel agents—had a significantly longer median overall survival (OS) than patients diagnosed earlier (Table). Improvement in outcomes with new therapies has been especially noteworthy in younger individuals. The study found that the prolongation of survival reported from 1996 to 2006 occurred predominantly among those patients aged <65 years (Table).2 This observation underscores the importance of using novel agents to extend the productive lives of younger MM patients.

However, these treatment advances have come at a price. Drug utilization costs for new medications are substantially higher than those for conventional chemotherapies.3 Moreover, higher drug costs have been added to another, relatively recent cost driver, autologous stem cell transplantation (ASCT),4 which can cost approximately $36,000 to $88,000.5 The impact of adverse events with novel agents—notably peripheral neuropathy (PN) and venous thromboembolism—must also be factored into the determination of value.4

Newer therapies thus yield better outcomes, but at a higher cost, demanding a recalibration of the value equation in MM. This recalculation remains incomplete, however, because pharmacoeconomic analyses across clinical settings are as yet insufficient. Nevertheless, cost and life-quality studies of individual drugs, along with available comparative data, do provide guidance on the value of therapy with novel agents.

HRQoL with VMP Versus MP

Health-related quality of life (HRQoL) with bortezomib-based therapy was evaluated in the phase 3 VISTA trial, a randomized study (N=682) comparing bortezomib/melphalan/prednisone (VMP) versus melphalan plus prednisone alone (MP) in transplant-ineligible patients with myeloma.6 HRQoL assessments were performed for a subset of 649 patients, and baseline HRQoL on all domain scores was similar between the VMP and MP groups. Very early in therapy, between cycle 3 and cycle 6, life-quality domain scores were generally worse with VMP-treated patients. However, HRQoL scores subsequently improved in the VMP group, and, by the end of treatment, HRQoL was comparable to baseline in both treatment groups. The transitory decline in HRQoL with VMP was attributable to the incremental toxicities of adding a third drug. Clinically meaningful improvements in some aspects of HRQoL occurred when patients attained response, with a trend of steady improvement in HRQoL after the onset of complete response (CR). This finding is important, since a significantly greater proportion of patients treated with VMP attained CR than did patients treated with MP (30% vs 4%; P<.001).6,7

OVERVIEW

The therapeutic paradigm for multiple myeloma continues to evolve at a rapid pace. The goal of this newsletter series, published by the Association for Value-Based Cancer Care™, is to provide readers with recent clinical advances in myeloma treatment, as well as stakeholder perspectives on how emerging data can be used to promote high-quality, cost-effective care. Each supplement will discuss a specific topic to be considered when developing value-based strategies. In this third newsletter, we explore the pharmacoeconomic analysis of novel therapies being used to treat the disease.

STAKEHOLDERS’ PERSPECTIVES

Addressing Ongoing Challenges in the Treatment of Myeloma .................................................................5
By Suzanne R. Fanning, DO
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Analyzing the Value of Therapy in the Era of Novel Agents .................................................................6
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NR indicates not reported; OS, overall survival.

IV Versus SC Bortezomib

On the basis of recent clinical evidence, cancer centers are transitioning from intravenous (IV) to subcutaneous (SC) bortezomib to reduce the incidence and severity of PN. A phase 3 trial conducted by Moreau and colleagues (N=222) demonstrated that the overall incidence of this toxicity was 53% with IV bortezomib versus 38% with SC bortezomib ($P=.044$), with an incidence of grade 3 or worse neuropathy of 16% versus 6%, respectively ($P=.026$).\(^8\) In a time-efficiency analysis of SC versus IV bortezomib (N=92), Barbee and colleagues reported less chair or visit time and greater patient satisfaction with the SC route of administration (Figure 1).\(^9\)

Cost-Effectiveness Studies: Bortezomib- and Lenalidomide-Based Therapies

The United Kingdom’s National Institute for Health and Care Excellence, which makes recommendations for the National Health Service (NHS), did not initially endorse bortezomib for the retreatment of myeloma, because a 2006 pharmacoeconomic analysis failed to support the cost-effectiveness of this drug relative to dexamethasone in patients with relapsed disease.\(^10\) Subsequently, a risk-sharing arrangement between NHS and the manufacturer did pave the way for NHS to allow bortezomib use in the relapsed setting.\(^11\)

Therefore, according to this analysis, MPR without subsequent lenalidomide maintenance is not a cost-effective strategy.

A study conducted in England and Wales by Brown and colleagues used a simulation model to evaluate the cost-effectiveness of lenalidomide plus dexamethasone (Len/Dex) versus dexamethasone alone in patients with relapsed/refractory MM who had been treated with at least 1 prior therapy.\(^12\) The simulation model suggested an incremental improvement in time to progression of 9 months, an increase of 3.2 life-years, and an additional 2.2 quality-adjusted life-years (QALYs) with Len/Dex compared with dexamethasone alone. The study reported an incremental cost-effectiveness ratio (ICER) for Len/Dex of £30,153 (≈$46,924) per additional QALY gained. Investigators concluded that the 2-drug combination is cost-effective, even though the drug cost for Len/Dex was much higher than for dexamethasone alone.

Kim and colleagues analyzed data from the MM-015 study (N = 459), which compared the cost-effectiveness of MP versus melphalan/prednisone/lenalidomide (MPR) versus MPR plus lenalidomide maintenance (MPR-R) in newly diagnosed MM patients ineligible for transplant.\(^13\) Median progression-free survival was 13 months for MP, 14 months for MPR, and 31 months for MPR-R in this study. MPR-R was the most expensive of the 3 arms in terms of total cumulative costs, with an average cumulative cost per patient of $231,314, compared with $166,211 for MPR and $17,972 for MP. However, when the efficacy of each regimen was taken into account, the investigators reported that the average cumulative cost per progression-free survivor for MPR greatly exceeded that for both MPR-R and MP ($1,540,139 vs $516,322 vs $309,346), while the cost difference between MPR-R and MP was less distinct. Therefore, according to this analysis, MPR without subsequent lenalidomide maintenance is not a cost-effective strategy. MPR-R is more likely to be cost-effective, although this regimen incurs substantial cost with no OS benefit yet reported.\(^11\)

Three studies have compared the pharmacoeconomics of bortezomib monotherapy versus Len/Dex in the relapsed/refractory setting, with conflicting results.\(^15\) This comparison is instructive, although it does not model current clinical practice, which often utilizes multidrug bortezomib therapy for relapsed and refractory patients. Borrello and colleagues reported that, despite similar drug costs for the 2 therapies, bortezomib monotherapy had a higher total treatment cost than Len/Dex.\(^15\) Higher cost for bortezomib was the result of IV administration (compared with oral treatment with Len/Dex), lab tests, other medical resource costs, and the management of adverse events. Conversely, Möller and colleagues found that, in Norway, both life-years and QALYs were higher with Len/Dex than with bortezomib (life-years, 4.06 vs 3.11; QALYs, 2.95 vs 2.19, respectively).\(^17\) ICER for Len/Dex was NOK...
Figure 2. Lifetime direct medical costs: VMP versus MPT versus MPR-R.20


247,078 per QALY gained with this regimen. Hornberger and colleagues reported divergent results in Sweden as well.18 In this study, QALYs for bortezomib monotherapy, Len/Dex, and dexamethasone alone were 2.95, 2.91, and 2.26, respectively. Bortezomib increased both costs and QALYs relative to dexamethasone. Mean incremental cost per QALY of bortezomib compared with dexamethasone was SEK 902,874. Bortezomib showed a cost-savings with respect to Len/Dex.18

A health technology assessment by Picot and colleagues studied the pharmacoeconomics of multidrug regimens, including chemotherapy (melphalan or cyclophosphamide) and a novel agent (bortezomib or thalidomide), in 5 randomized controlled trials of newly diagnosed, transplant-ineligible myeloma patients; the comparator in these trials was MP.19 Two regimens, VMP and melphalan/prednisone/thalidomide (MPT), proved more effective than MP. In addition to its higher efficacy, MPT was also assessed as being more cost-effective than VMP or a regimen of cyclophosphamide/thalidomide/attenuated dexamethasone (CTDAs). These observations must be tempered by the fact that only 1 of the analyzed studies evaluated the VMP regimen and 1 evaluated CTDa, while 3 evaluated MPT.

A more recent analysis by Garrison and colleagues reported that VMP would most likely be a more effective-cost-effective frontline regimen compared with MP, MPR-R, and MPT for transplant-ineligible patients.20 This study, which based efficacy findings on 3 key clinical trials,7,14,21-23 found that 3%-discounted lifetime direct medical costs were lowest with VMP and highest with MPR-R (Figure 2). This result is consistent with observations that lenalidomide can be a strong cost driver in therapy, with a historically high acquisition cost,7 although not all studies have reported a striking differential in acquisition cost with Len/Dex versus bortezomib.15,16

The Value Decision

Pharmacoeconomic analysis of drug therapy in MM continues to evolve but still remains incomplete in 2013. Moreover, such an analysis is complicated by the complex nature of myeloma care, which, along with drugs, includes ASCT and supportive care with bisphosphonates.24,25 For example, part of the current debate on the relative merits of early transplant (immediately after first induction) versus late transplant (at first relapse) hinges on the issue of comparative cost. A recent decision-tree analysis favored early ASCT from a cost perspective, but more evidence is needed to determine the clinically optimal choice.24

Thus far, there is no expert consensus on which therapeutic paths offer the highest value in myeloma care. However, 2 reviews from Italian research groups suggest factors to consider in making the value assessment.26,27 The first study, by Koleva and colleagues, showed that, whereas the total average annual costs of myeloma care were comparable between patients aged <65 years and those >65 years, the cost of the antimyeloma drugs themselves was significantly higher in the elderly age group.26 Because older patients are less likely than younger ones to incur costs for ASCT, these observations must be tempered by the fact that only 1 of the analyzed studies evaluated the VMP regimen and 1 evaluated CTDa, while 3 evaluated MPT.

A more recent analysis by Garrison and colleagues reported that VMP would most likely be a more cost-effective frontline regimen compared with MP, MPR-R, and MPT.

Conclusion

Pharmacoeconomic evidence in myeloma care is fragmented, with no definitive comparisons among current regimens.28 The frequency of economic evaluations has actually declined in the past decade—a concerning trend, given the rapid rate of new drug approvals and the growing pressure to contain healthcare costs. Although no specific strategies have emerged as the highest-value approach to care, stakeholders can make indirect comparisons of available data—keeping in mind that there is always more risk in weighing data from studies differing in design and extending the time to progression with effective treatment may reduce the number—and consequently, the cost—of subsequent treatments. For instance, investigators in the VISTA and MM-015 trials showed that VMP and MPR-R, respectively, delayed progression relative to MP,7,14 suggesting the potential to delay the need for treatment of relapse in older, transplant-ineligible populations. The second study, by Messori and colleagues, reviewed the cost-effectiveness of regimens that included thalidomide, lenalidomide, or bortezomib.27 This evaluation did not differentiate value among these 3 drugs; rather, it found that in newly diagnosed MM patients, whether undergoing ASCT or not, use of any novel agent conferred an average additional 10 to 12 quality-adjusted life-months (QALMs); gain in QALM is only slightly less when such drugs are used for the treatment of relapsed and refractory disease. These observations suggest that including a novel drug in the regimen offers value, not only upfront, but also in the relapsed/refractory setting.
sample size. Nevertheless, studies to date provide reassurance that including novel, molecularly targeted drugs is a value-based approach to care. It remains to be seen which specific regimens provide the most value in distinct patient populations.

Dana Delibovi contributed to the development of this article.

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Addressing Ongoing Challenges in the Treatment of Myeloma

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The main article in this supplement highlights our increasing awareness of the rising cost of managing both treatment-naive and relapsed patients with multiple myeloma (MM). Through cost, quality of life, and comparative data, the author concludes that the use of novel, molecularly targeted drugs is a value-based strategy. An ongoing dilemma, however, is how to treat each individual patient in the most effective and cost-efficient manner. Do we stratify by age, knowing that younger patients have been shown to derive the most benefit? Do we stratify by risk profile as determined by fluorescence in situ hybridization analysis or conventional cytogenetics? These are just a few of the many questions that remain without answers.

Our challenge, as providers of care, is to treat patients regardless of the paucity of phase 3 randomized clinical trials available to date. Without direct comparisons of doublet or triplet regimens in similar patient populations, we are unable to definitively determine if spending more money to achieve a deeper response is truly cost-effective. These are essential issues to consider as an increasing number of patients are deemed transplant eligible. In this patient population, we know that chemosensitive disease pretransplant is associated with higher event-free survival (EFS) and overall survival (OS) rates. Therefore, initial response in these patients is critical to the success of subsequent treatment.

The role of autologous stem cell transplantation (ASCT) in myeloma is also a frequently debated topic. As a practitioner of stem cell transplant, I discuss with my patients the improved response rates, EFS, and OS associated with this line of therapy. As a practitioner of stem cell transplant, I discuss with my patients the improved response rates, EFS, and OS associated with this line of therapy. However, we do not have a randomized trial that shows superiority with regard to progression-free survival without ASCT. At present, an enrolling trial by Richardson and colleagues is looking at induction with a regimen of lenalidomide/bortezomib/dexamethasone (RVD) followed by either ASCT with lenalidomide maintenance or additional RVD followed by lenalidomide maintenance. Once this trial has been completed, we will have a better understanding of the value of transplant in the era of novel therapies. As already mentioned, ASCT has associated costs of its own, making determination of effectiveness paramount.

The main article also discusses the importance of health-related quality of life (HRQoL). Too often, this is an overlooked topic in cancer treatment—especially among patients with hematologic malignancies. Given that MM remains an incurable disease, we are obligated to explore this issue for our patients. In a population-based study by Mols and colleagues, a very high symptom burden and low HRQoL were reported among myeloma patients followed up to 10 years after diagnosis. Intuitively, the authors concluded that the goal should be to maximize disease control while minimizing symptoms. As physicians, this happy medium can seem elusive. In the VISTA trial, a trend toward improved HRQoL was noted in patients attaining a complete response after treatment with bortezomib/melphalan/prednisone. For the remainder of patients, however, HRQoL transiently declined with the 3-drug combination. Ideally, indicators of early response (eg, 50% reduction in M-spike after 2 cycles of treatment) are needed to minimize the toxicity of combination regimens in patients with less robust response.

Cost efficiency does not always equate to best management in all circumstances, neither does the most expensive therapy necessarily result in optimal outcomes.

We are fortunate to be living in an era of dramatic cancer treatment development, and it is incumbent upon us to use these therapies wisely. Whereas cost efficiency does not always equate to best management in all circumstances, neither does the most expensive therapy necessarily result in optimal outcomes for all patients. We are challenged with the sorting out of these details, but I have no doubt the current hematology/oncology community is up to the task.

References
Analyzing the Value of Therapy in the Era of Novel Agents

A significant proportion of patients with the disease are ineligible for ASCT, which may place even more importance on the choice of initial therapy.

In the maintenance setting, investigators in the phase 3 MM-015 trial compared MP versus melphalan/prednisone/lenalidomide (MPR) versus MPR plus lenalidomide as maintenance (MPR-R) in nontransplant patients in an attempt to assess the value of extending treatment. Interestingly, lenalidomide maintenance (MPR-R regimen) improved progression-free survival (PFS) by 66% compared with no maintenance, regardless of patient age.

The use of single-agent novel therapy has been shown to cost more than $300 per day, depending on the dose being used.

Although overall survival benefit has yet to be seen in the MM-015 trial, Kim and colleagues were able to assess the value of using lenalidomide as maintenance therapy, as discussed in the main article in this supplement. The cost of MPR without lenalidomide maintenance was $166,000, and MP was least costly at $18,000. As expected, MPR-R was the most expensive regimen by drug cost alone at more than $230,000. Given current lenalidomide costs, one may have expected the MPR-R drug cost to be even higher based on the difference in PFS of 14 months for MPR and 31 months for MPR-R. However, the study concluded that the cost per progression-free survivor for MPR greatly exceeded that for both MPR-R and MP. In fact, according to the analysis, the cost of MPR per progression-free survivor was 3 times that of MPR-R and 5 times that of MP. This analysis demonstrated the cost value of MPR-R compared with MPR. However, within this analysis, based on the relative inexpensiveness of MP, the value of MPR-R compared with MP was not demonstrated, despite the large difference in median PFS (31 months for MPR-R vs 13 months for MP).

Managed care professionals can appreciate the economic analysis of these agents, as it can be difficult to get past the "sticker shock" of the cost of monthly therapy. Manufacturers should also consider these types of analyses when determining the price of their agents. The factor that makes the question of value even more difficult is the use of multiple novel agents, not only in the initial setting, but in later phases of treatment (ie, maintenance and salvage therapies). Hopefully, long-term data from clinical trials will be useful in our shared goal of providing patients with the best access to cost-effective therapy.

References
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MISSION

The mission of AVBCC is to provide a forum for payers, providers, and the entire oncology team to consider and evaluate the cost-value issues particular to cancer treatments and their impact on patient care and outcomes. This unique focus is achieved through discussions and collaborations with those involved in evaluating therapies, treating patients, and paying for care.

VISION

The vision of AVBCC is to provide a unique forum for all stakeholders to discuss, consider, and evaluate the cost-value issues particular to new cancer therapies, as they relate to all cancer patients so they may benefit with optimal outcomes.

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