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Efficient Allocation of Novel Agents in Multiple Myeloma: A Work in Progress

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Disclosures of potential conflicts of interest may be found at the end of this article.

Payers of healthcare worldwide are concerned with the rising costs of healthcare. The costs of oncology care alone have increased [1], with the size of the oncology market having more than doubled since 1997, reaching $35 billion in 2006 [2]. Scientific advances, particularly the development of targeted agents, are a contributing factor to the rise in oncology costs. Patient outcomes have improved, but at significantly higher costs compared to conventional therapies. Over the past 40 years the median monthly costs of cancer drugs have risen from less than $100 in 1965–1969 to more than $5000 in 2005–2009 (2007 prices) [3], with cancer drugs now accounting for 10–20% of total expenditures for cancer and 5% of total drug expenditures [4].

In multiple myeloma, the past decade has brought about the introduction of thalidomide, bortezomib, and lenalidomide, with additional novel agents recently approved or in the pipeline [5, 6]. Together with improvements in stem cell transplantation and supportive care [7, 8], their use has extended the expected overall survival from diagnosis [9]. However, the gains in health are not distributed equally, with some patients' health improving more significantly than others [10]. Given the substantial impact of these novel agents on the healthcare budget, a better understanding of their relative cost-effectiveness would aid in their efficient allocation. The key questions in multiple myeloma, addressed by two articles in this month's issue [11, 12] include how much do novel agents cost? What are their health benefits? Can their use be more efficiently allocated? Using different approaches, both studies performed an economic evaluation to come to somewhat similar conclusions.

Teitelbaum et al. estimated the real-world costs of novel agents based on patient-level claims data from a large U.S. health plan. This study is impressive in the large number of patients that were included, encompassing a total of 4,836 treatment episodes in 2,642 patients. The one-year costs of novel agent treatment episodes were estimated after correcting for differences in the patient population. The results were not surprising as they confirm the significant budget impact of novel agents from previous studies [13–16]. Interestingly, they are the first to report that that the costs of bortezomib-based episodes ($112,359) were similar to those of non-novel agent-based regimens ($112,060), while thalidomide-based ($130,468) and lenalidomide-based regimens ($159,158) were significantly higher. Previous studies outside the U.S. found that thalidomide-based regimens were less costly compared to bortezomib and lenalidomide [13–15]. The reasons for this discrepancy include differences across studies in unit price for generic versus branded thalidomide, treatment dosages and duration, and patient condition. The authors also report similar frequency in ambulatory visits by novel agent in first-line treatment episodes, suggesting no perceived benefit of oral therapy (i.e., thalidomide and lenalidomide) over intravenous administration (i.e., bortezomib) in terms of patient visits in newly diagnosed patients since frequent patient assessments are performed regardless of regimen. There was, however, a reduction in the number of predicted ambulatory visits during lenalidomide in the relapsed/refractory setting, which was also found previously [14], and is likely due to less frequent patient visits for treatment-related adverse events. The authors also provide new insight into the economic burden of care from the patient perspective. Patient out-of-pocket costs were found to be significantly higher during thalidomide and lenalidomide episodes and were attributed to the coverage gap for outpatient drugs in Medicare Part D. This is an important finding revealing inequity in patient cost burden that could adversely impact access to care and health outcomes for many patients.

This study, however, tells only part of the story as costs were limited to one year instead of the entire treatment episode, and no health benefits were accounted for, thus leading to false conclusions about value for money in the case of more costly regimens that offer benefits past one year. The strength in large patient numbers may also be a limitation because heterogeneity conceals differences in benefits within narrowly defined prognostic groups.

To address the question of efficiency for these drugs, it is necessary to consider their total costs and health benefits beyond one year, especially given differences in mode of administration, treatment duration, and adverse event profile. Garrison et al. fill a consistent yet important evidence gap [17, 18] by addressing this question for a more narrowly defined group. They are the first to perform a modeling study to evaluate the cost-effectiveness of all three novel agents in combination with melphalan prednisone (MP) in newly diagnosed transplant-ineligible patients. Using results from various randomized controlled trials [19–22], the authors compared the costs, life-years (LYs) and quality-adjusted life years (QALYs) over a period of 20 years for MP plus bortezomib (VMP), thalidomide (MPT) and lenalidomide with maintenance (MPR-R)

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in a decision model. The results show VMP to be more effective than MP (4.187 LYs/2.994QALYs versus 2.864LYs/2.049QALYs) but more costly ($119,102 versus $63,294). Compared to MPT, VMP was further found to be cost-saving (-$23,350) and slightly more effective (0.047LYs/0.043 QALYs). Incremental costs (-$129,256) and effects (0.778LYs/0.566QALYs) were even higher when compared to MPR-R though increased costs were mainly attributable to additional maintenance therapy. Based on these findings, adding bortezomib to the MP regimen was argued to be more cost-effective than adding thalidomide or lenalidomide in transplant-ineligible patients. A preference for VMP over MPT is in contrast, however, to previous findings in the U.K [23]., but is explained by the differences in modeling methods and unit costs for thalidomide.

Then again, are the results of modeling studies robust? Garrison et al. 's model was based on a number of assumptions, potentially creating bias. Cost estimates were not based on actual patient data but instead on assumptions regarding resource use and unit costs and a budget impact model from independent data. The effectiveness was calculated for VMP and MP using patient-level trial data, whereas published trial results were used for MPT and MPR-R. The analysis for MPR-R was further weakened since the trial results were immature (i.e., interim analysis). To obtain a more robust estimate of cost-effectiveness for MPR-R, a future study could incorporate the results of a currently ongoing phase III trial (E1A06) comparing MPT-T and MPR-R.

Readers may also question the possibility of bias in the results favoring bortezomib given that both studies were funded by the manufacturer. To their credit, the authors disclosed funding and attempted to address a number of methodological weaknesses along with providing transparent assumptions. We nonetheless urge readers to interpret the results in light of the methodological limitations discussed above. Moreover, readers should acknowledge the need for additional public funding of pharmacoeconomic and outcomes research studies. The funding party of these studies typically depends on the type of question asked, who is asking it, and perhaps disease burden [24]. A more collaborative effort has the advantage of addressing multiple objectives for a broader set of treatment options or care processes instead of simply providing evidence of superiority for treatment options only relevant to stakeholders with a financial interest [25]. Including additional stakeholder perspectives also creates access to more generalizable data thus potentially improving methodological quality. To judge whether the implications of these and future studies are influenced by the funding source, there are standardized methodological guidelines available [26] for those performing, reporting, and evaluating pharmacoeconomic studies.

It should be noted that the treatment combinations assessed in these studies may soon be irrelevant for certain groups as the treatment paradigm shifts toward multiple novel agent combinations. Combinations of bortezomib and thalidomide [27, 28] or lenalidomide [29, 30] have both shown improved response rates, with the former also improving progression-free survival. However, neither combination demonstrated superior overall survival. Because no trials have compared these rather expensive combinations to similarly effective and less toxic combinations, some argue that these options may only be relevant for high-risk patients who do not benefit from current options [31], which presents an opportunity for future studies assessing the value of novel agents.

To conclude, where can the use of these drugs be assumed efficient? At the moment, upfront VMP could be cost-effective compared to MPT or MPR-R in transplant-ineligible patients from a U.S. healthcare payer perspective. This finding requires confirmation with patient-level data, preferably from daily practice, which will require active interdisciplinary collaboration and the sharing of existing data [32]. The value of observational data should be emphasized for future studies since costs were much higher when based on real-world data, demonstrating that studies relying on assumptions for costs are susceptible to underestimation.

This question remains unanswered for newly diagnosed transplant-eligible patients as well as for the relapsed/refractory setting since existing studies are either outdated [33] or not generalizable to the U.S [34, 35]. Future research in this area should move away from addressing efficiency-related questions in heterogeneous groups and instead focus on subgroups with homogenous prognoses, particularly by incorporating prognostic risk markers [36], as well as treatment sequence [37]. When drawing conclusions from current and future economic studies regardless of indication, it is important that readers keep in mind that efficiency in one setting may not transfer to another, due not only due to differences in study methodology but also, and perhaps more importantly, to differences in patient care, prognosis, and policies impacting access to care.

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Editor's Note: See the related articles on pages 27–36 and 37–45 of this issue.