Next-generation multiple myeloma treatment: a pharmacoeconomic perspective

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Introduction

There have been major advances in the last 15 years in the diagnosis and treatment of multiple myeloma.1,2 Overall survival has improved remarkably during this period driven by discovery of several new active drugs. However, as in every other malignancy, new drugs come with a hefty price tag: almost every approved cancer drug in the last few years costs more than $100,000 per year in the United States, and myeloma treatments are no exception.3,4 Even the price of old drugs such as melphalan has increased greatly over time. The problem of cost and affordability is amplified in myeloma in 3 ways. First, the disease requires multidrug combinations, increasing the already expensive cost of care to unsustainable levels.5,6 Second, treatments are usually continued until progression in the form of “continuous therapy” or “maintenance therapy,” ensuring that high costs are not a temporary problem but rather an unrelenting dilemma for the patient.7,8 Third, as survival has improved markedly (median of >7-10 years for standard-risk patients), the cumulative costs of care over the lifetime of a patient are exorbitant.9

The high cost of cancer care not only impacts the patient directly but also has an impact on society in the form of rising premiums, taxes, or both. In many countries, high costs limit access to effective drugs, as neither the health care system nor the individual patient can afford these costs without cutting back on other essential needs.10-12 In this Perspective, we outline the current state of myeloma therapy and discuss the costs involved. We summarize the primary reasons why cancer drugs are so expensive, and list some measures that are required to lower cost. We also propose potential ways in which costs can be reduced in myeloma while still delivering high-quality care, and provide recommendations for strategic clinical trials.

Modern therapy of myeloma

The treatment of myeloma varies across the world depending on many factors, including access to new drugs and resources, cost constraints, and treatment philosophy. The general approach to therapy (Figure 1) is summarized in the following sections, and is essential to the discussion on cost and strategies to deliver cost-effective care.13 Importantly, the approach outlined is fairly uniform across the world, but the availability of new drugs may reduce the number of options in many parts of the world. Major advances are summarized in Table 1.14-26

Initial therapy

Patients who are candidates for ASCT are treated with induction therapy for approximately 3 to 4 cycles with a triplet regimen consisting of bortezomib and dexamethasone combined with either lenalidomide (VRD), thalidomide (VTD), or cyclophosphamide (VCD), followed by stem cell harvest.13 After harvest, patients proceed to ASCT, followed by maintenance therapy for at least 1 to 2 years. Selected patients with standard-risk myeloma may defer ASCT until first relapse.27-29 The use of maintenance varies across countries based on drug approval and availability. Generally, lenalidomide is the drug of choice for maintenance.16,17 although some experts prefer bortezomib-based maintenance for patients with intermediate- and high-risk disease.30 Patients who are not candidates for ASCT are treated with either a triplet regimen for 12 to 18 months or alternatively with Rd until progression.31 The choice of the triplet regimen varies, but in general melphalan-based regimens are being replaced by newer regimens such as VRD or VCD.

Treatment of relapsed myeloma

Almost all patients with myeloma relapse after initial therapy, at a median duration of 4 years after ASCT plus maintenance, or ~2.5 years without ASCT.15,31 The disease is then characterized by multiple relapses and remissions, with the number of remissions dependent on the available treatment options. In the last 5 years, several new drugs have been introduced into clinical practice greatly
expanding treatment options. These include carfilzomib,19 pomalidomide,20 panobinostat,21 elotuzumab,22 daratumumab,23,24,32 and ixazomib.25 All of these drugs have secured the approval of the US Food and Drug Administration (FDA) and are available in the United States. However, the availability of these drugs in other countries is varied depending on the regulatory approval status. In general, due to regulatory and/or economic reasons, most of these drugs have limited availability in many parts of the world. Nevertheless, the availability of multiple active drugs has resulted in numerous combinations that can be used to treat relapsed disease. A patient refractory to 1 regimen may respond to another.

The choice of a treatment regimen at relapse is complex. The main factors that influence the selection of a specific regimen depend on whether the relapse occurs on or off therapy, the type, nature of response, and tolerability of the prior regimen, number of prior lines of therapy, aggressiveness of the relapse, and the physical condition of the patient.33 These considerations are taken into account at each relapse. In patients who are fit, it may be possible to try numerous regimens sequentially.

Figure 1. Current treatment of multiple myeloma. (A) Newly diagnosed and (B) relapsed. *Or similar bortezomib-based triplet. **Bortezomib may be preferred for intermediate- and high-risk patients. †Consider salvage ASCT in patients eligible for ASCT. ¶Any of the regimens listed for first relapse that the patient has not previously been exposed to. ASCT, autologous stem cell transplantation; DRD, daratumumab, lenalidomide, dexamethasone; DVD, daratumumab, bortezomib, dexamethasone; ERD, elotuzumab, lenalidomide, dexamethasone; IRD, ixazomib, lenalidomide, dexamethasone; KRD, carfilzomib, lenalidomide, dexamethasone; PD, pomalidomide plus dexamethasone. Rd, lenalidomide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone.

Cost considerations

Current diagnosis and treatment of myeloma is expensive, not just due to the cost of specific new drugs but due to several factors that play a role in diagnosis, staging, management, and monitoring.

Diagnostic and monitoring costs

Bone disease is the main cause of morbidity in myeloma, and accurate detection is critical for diagnosis and assessment of response. Although bone involvement can be detected on routine skeletal radiographs, we increasingly need whole-body low-dose computed tomography, magnetic resonance imaging, or fluorodeoxyglucose positron emission tomography/computed tomography scans to evaluate disease at multiple points during the disease course.1,34,35 Not all new imaging tools are needed at the same time for each patient, and guidelines on optimal use have been proposed by the International Myeloma Working Group (IMWG).35 Nevertheless, these are expensive imaging modalities that add to the cost of care. Similarly, the costs of standard bone marrow examination in myeloma have risen considerably due to the need for studies such as fluorescent in situ hybridization (FISH) that are required for molecular classification and risk stratification.36,37 FISH studies are needed to identify patients who have high-risk cytogenetic features such as gain(1q), del(1p), del(17p), and translocations t(14;16), t(4;14), and t(14;20).38-41 The Revised International Staging System (R ISS) for myeloma requires assessment of myeloma cytogenetics by FISH or equivalent method.42 The success of myeloma therapies has enabled the achievement of deep responses, prompting the development of methods to detect minimal residual disease such as next-generation molecular sequencing and next-generation flow cytometry.43 Clearly, advances in bone imaging and accurate molecular cytogenetic risk stratification provide clinical benefit and are needed for the optimal management of myeloma. We do not question their value. At the same time, it is important to recognize
how the costs of new drugs are not the only economic issue of concern to myeloma patients. In some countries where the cost of care is borne directly by the patient (out-of-pocket care), it is likely that compromises occur and some essential tests are omitted. Even in countries with third-party payment systems, the extent and nature of testing may be restricted based on what can be reimbursed.

Cost implications of current therapy

The modern treatment of myeloma discussed earlier is expensive. The standard triplet combination of VRD can cost more than $150 000 per year (US dollars; all costs estimated from www.goodrx.com). Four cycles of VRD followed by ASCT is no different. Once initial therapy is completed, at current market prices in the United States, maintenance therapy with lenalidomide will cost approximately $100 000 per year.

In patients undergoing ASCT, the median time to progression following induction, transplantation, and maintenance is ~4 years; this equates to an overall cost of initial therapy in excess of $500 000. But this is only the beginning: the rapid progress over the last decade means that society still pays in the form of increased premiums and taxes. Furthermore, although insurers (or governments) may pick up the bulk of the cost, most of these costs are passed on to patients in the form of increased copays and denial of coverage. Even the well-insured are not immune to these costs. They may be impacted by high copays or denial of coverage. For example, trials are evaluating the promise of KRD as initial therapy; this regimen is ~1.5 to 2 times more expensive than VRD. But more important in terms of cost is the likely addition of daratumumab, a highly active monoclonal antibody to various triplet regimens currently in use for the treatment of myeloma to create quadruplets that could cost in excess of $300 000 per year.

But there is more: several other promising agents have shown single-agent activity in myeloma and will likely be approved for the treatment of the disease in the future. These include: isatuximab, a CD38 monoclonal antibody; marizomb, a new proteasome inhibitor; oprozomb, an oral proteasome inhibitor related to carfilzomb; filanesib, a kinesin spindle protein inhibitor; dinaciclib, a cyclin-dependent kinase inhibitor; venetoclax, a selective B-cell lymphoma 2 inhibitor; and LGH-447, a pan proto-oncogene serine/threonine-protein kinase inhibitor (Table 1). Once approved, these new drugs will greatly increase the number of rational combinations that are possible, as well as the inevitable associated costs. This is unsustainable.

We do not lament the advances that have occurred in myeloma. We welcome and embrace them. They have changed the face of myeloma, and brought hope and even the prospect of cure to myeloma patients. However, we also recognize that, at current costs, these advances will be a reality only to a small proportion of myeloma patients may not be able to avail of these advances because it is unlikely that either government-funded health care programs or individual patients will be able to afford the best of what we experts can design to treat the disease. Even more unfortunate is the fact that many myeloma patients in many parts of the world will not even be aware of the spectacular results that are possible with modern myeloma therapy, let alone have access to them.

Reasons for high cost of cancer drugs

The high cost of drugs to treat myeloma is reflective of a bigger problem that involves almost all new oncology drugs. Why are cancer drugs so expensive? And, what can we do about it? The high cost of cancer drugs is related to numerous factors. These factors are present in other disease settings as well but are amplified considerably in cancer (Table 2). First, it is expensive to move findings from bench to bedside in cancer, and perform all the regulatory studies needed to gain regulatory approval. Many drugs fail, due to the very nature of advanced cancer. Pharmaceutical companies attempt to regain investment by adding costs of development of both successful and unsuccessful products on the newly approved drug. Second, because most cancers such as myeloma are not curable, patients need to be treated with each approved agent (sequentially or in combination). For example, the
Table 2. Reasons for high cost of cancer drugs and possible solutions

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<th>Reasons and solutions</th>
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<tr>
<td>Why are cancer drugs so expensive?</td>
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<tr>
<td>• High cost of drug development</td>
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<td>• Existence of virtual monopoly; lack of free market competition</td>
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<td>• Sustaining monopoly with &quot;new and improved&quot; versions of a drug as patents expire</td>
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<td>• Willingness of patients to pay high costs even for marginal improvements in outcome</td>
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<td>• Higher reimbursement to providers when more expensive drugs are administered</td>
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<td>• Legal barriers that prevent the FDA from taking economic and cost-effectiveness considerations into account when approving new drugs</td>
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<td>• Laws that prevent CMS from being able to negotiate the price of new drugs</td>
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<tr>
<td>• Prohibition of importation of drugs for personal use</td>
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<td>• Resistance to change in policies from pharmaceutical companies and from professional and patient support organizations who receive financial support from pharmaceutical companies</td>
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<tr>
<td>What can we do about it?</td>
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<tr>
<td>Value-based reimbursement and pricing</td>
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<td>• FDA, CMS, or other agency should be able to negotiate the sale price based on the incremental value provided by the drug as is done by health authorities in Canada and Europe</td>
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<td>• PCORI should be authorized to allow cost-effectiveness as a metric to compare relative value of treatments</td>
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<td>• Support organizations such as Institute for Clinical and Economic Review which evaluate the cost-effectiveness and affordability of new treatments</td>
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<td>Negotiation of prices and formulary control</td>
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<td>• CMS should be authorized to negotiate cost and have formulary control</td>
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<td>• Strong advocacy and a patient-driven grass-roots movement for the required changes in federal law</td>
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<td>Increase market competition</td>
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<tr>
<td>• Allow importation of drugs for personal use</td>
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<td>• Facilitate easier approval of generics</td>
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<td>• Selectively invoke compulsory licensing provisions</td>
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<td>New modalities for drug development</td>
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fact that there are several active myeloma drugs does not mean that a patient does not need to try daratumumab at some point in the disease course. This in effect makes each drug a virtual monopoly.51 Third, even as the monopoly ends as patents expire, “new and improved” versions of an approved drug appear on the market. At this time, the older drug tends to be viewed as substandard treatment thereby perpetuating the situation. In myeloma, there is now a pressure to consider newer proteasome inhibitors (carfilzomib and ixazomib) in favor of bortezomib.59 Although there is a role for these newer drugs, there are no good data indicating that trying them after bortezomib fails would be any less effective. But with poorly designed trials it is possible to create an aura that the older drug is inferior. Fourth, a diagnosis of cancer carries grave consequences and patients often want to try every potentially useful drug, even if they are expensive and provide only marginal improvements in outcome. More importantly, in most developed countries including the United States, patients are not the primary payers for the drug. This makes high prices easier to sustain in the pharmaceutical sector compared with other economic sectors where the “client” has to make a choice to buy or not based on affordability.51 Finally, systems in the United States provide an incentive to administer more expensive chemotherapy and to keep prices high.55 This includes policies that allow higher reimbursement when more expensive drugs are administered, legal barriers preventing the FDA from taking economic and cost-effectiveness considerations into account when approving new drugs, laws that prevent the Centers for Medicare & Medicaid Services (CMS) from being able to negotiate the price of new drugs, and prohibition of importation of drugs for personal use.50,52,56 Attempts to change any of these policies are met with aggressive resistance not only from pharmaceutical companies (which is to be expected) but from many other quarters including professional and patient support organizations all of whom have significant financial conflicts of interest. In short, there are few allies in the fight to lower drug prices.

Reducing cost of cancer drugs

Value-based reimbursement and pricing

In many European countries, Canada, and Australia, regulatory approval is only the first step. The price of the drug is then subject to negotiation based on the value it provides.57,58 The value may be estimated by using strict criteria to determine the clinical added value compared with existing drugs. But in many countries, the value is defined either exclusively or partly by defining the efficiency of the drug (cost-results analysis). The value estimate is typically done by calculating the quality adjusted life year gained with the new treatment, and the incremental cost-effectiveness ratio (ICER).51 Thresholds are used in some countries such as the United Kingdom to decide access to market, but this carries the risk of drug restrictions. Elsewhere, the ICER is used for price negotiations. There is no consensus regarding ICER thresholds. The World Health Organization (WHO) has arbitrarily defined 3 times gross domestic product per capita as a reasonable ICER.59 At the price proposed by pharmaceutical companies, the ICER of all new myeloma treatments is far beyond this level. In the United States, there is no system to define fair price. The FDA approves drugs based on evidence of clinical benefit and safety. The magnitude of benefit is not taken into account to determine price.12 Thus, drugs that improve survival by only a few days or weeks can be priced at the same level as ones that provide a much larger degree of benefit. The United States needs laws that would allow value-based pricing.

The added value of a new drug should be the same in all countries if the comparator is the same. Therefore, methods for evaluating this added value should be the same and joint international assessments should be developed. Consensus regarding an acceptable ICER should be organized at least in countries with comparable gross domestic product. In the United States, organizations like the Patient-Centered Outcomes Research Institute (PCORI) should be authorized to take cost
into account when evaluating treatments. Currently, the PCORI, created by the Patient Protection and Affordable Care Act of 2010 (PPACA), is specifically prohibited from using cost-effectiveness measures in funding comparative effectiveness studies or in its recommendations. We also need to support private nonprofit organizations like the Institute for Clinical and Economic Review and other endeavors like DrugAbacus in their attempts to shine a spotlight on cost and value, as is done by health technology assessment institutions in Europe and other countries.

One argument against value-based pricing is that these measures will stifle innovation, and that they run counter to free-market principles. This argument cannot be farther from the truth. In fact, the current system in the United States allows a new drug to be marketed at a very high cost regardless of the value it provides. Thus, there is actually a disincentive for innovation. It is far safer and more lucrative to develop a “me-too” drug that is likely to succeed in a regulatory trial than to take the risk and develop a truly innovative product. Furthermore, the pricing of cancer drugs, unlike other commodities, is not representative of a “free-market” system. The checks and balances that make the free-market system work efficiently in other areas are absent in the oncology marketplace due to the monopolistic nature of new drugs, and the existence of laws that prevent standard free-market principles such as the inability to negotiate for low prices, the prohibition on importation, and the reimbursement model which involves third-party payers.

**Improved national guidelines**

Many cancer guidelines present a list of all possible or acceptable treatment options and primarily serve to ensure that patients have access to treatments that are felt to be effective for purposes of access or insurance coverage. Many guidelines include authors who have significant financial conflicts of interest. These guidelines seldom provide recommendations on how to provide the most cost-effective care. We need evidence-based guidelines that critically examine the available data, and provide clear recommendations not only on which regimens are preferred, but also on identifying regimens that should be avoided in a given setting if they lack adequate data on superiority compared with less expensive alternatives.

**Negotiation of prices and formulary control**

At present, the CMS is prevented by law from negotiating directly for the cost of cancer drugs administered through the Medicare Part D program. This law, passed by the US Congress in November 2003 in the dead of the night, required the CMS to purchase and provide prescription drugs to beneficiaries nationwide, while at the same time inexplicably prohibited it from being able to negotiate with pharmaceutical companies on the purchase cost of these drugs.

This, as expected, set up a situation ripe for annual price increases. Essentially, pharmaceutical companies could name their price and tag on year-after-year price increases. As long as it was not an egregious increase as occurred with Daraprim (Turing Pharmaceuticals) or EpiPen (Mylan), no one noticed. This needs to change. The single most important thing that we need to reduce cost is to authorize CMS to negotiate cost and have the ability to deny formulary addition if the cost is felt to be unacceptable. This will make the system in the United States similar to Europe and Canada. Importantly, it will eliminate the safety valve that pharmaceutical companies have which affects the cost of drugs around the world. The fact that prices can be increased in the United States to compensate any potential loss of market share probably enables pharmaceutical companies to walk away from price negotiations with smaller countries in Europe and elsewhere. This requires a major change in existing law and will not be possible without strong advocacy and a patient-driven grass-roots movement. In Europe, prices are negotiated at the national level, usually on the basis of the price in the United States, and different forms of rebates are proposed. However, the huge budget impact of recently introduced new drugs and drug combinations pushes payers to develop new ways for payment such as performance-based risk-sharing agreements where payments are linked to the actual results.

We also need to support recent efforts by the CMS to test indication-based pricing and fixed reimbursement amounts for closely related drugs in a given class. If the price of a drug is related to its added value, it should be lower in indications where the benefit for the patient is less evident. Currently, the price is the same for all indications whatever the results and the duration of treatment. There needs to be a renegotiation of the price in relation to the increased number of treated patients when new indications are authorized. Another possible solution might be to pay not for drugs but for the global treatment of a disease at a given stage.

**Increase market competition**

Several measures can be adopted to increase market competition which will result in lower costs the same way it works with other commodities. One approach to increase market competition is to allow importation of drugs from other countries for personal use. A second approach would be to make the approval of generics easier, and have international agreements that allow generics approved in selected countries automatic access to domestic markets.

Any concern about the quality of generics made by reputable companies is misguided, and will be in any case miniscule compared with the alternative of having large chunks of the affected population without access to effective drugs because of pharmacoeconomic reasons. We should also enact laws that prevent major pharmaceutical companies from engaging in a “pay-for-delay” strategy to delay the launch of a generic drug. A third approach would be for countries to invoke compulsory licensing provisions that are permitted under the Doha declaration of 2001. This mechanism in the interest of public health allows a country that is not able to negotiate a reasonable price to grant a license to a low-cost generic company to manufacture a life-saving drug that is still under patent protection for use within that particular country.

**New modalities for drug development**

Current drug clinical development usually involves phase 1 and 2 studies followed by large randomized phase 3 trials. When the mode of action or the target of a new drug is well defined in preclinical studies, it may be possible to more rapidly obtain proof-of-concept and positive results in selected groups of patients. Approval by the regulators might be decided sooner (so-called “adaptive licensing” or “adaptive pathway”). It necessitates new rules for approval with less clinical data, and requires postmarketing confirmatory studies.

**Strategies to reduce costs of myeloma treatment in clinical practice**

The solutions for high cost of cancer drugs, including those used to treat myeloma, appear difficult to achieve in a timely manner. What can be done in the meantime? Can we deliver cost-effective care without sacrificing efficacy in situations where access to the treatments outlined in Figure 1 is not feasible? For example, VRD has shown an overall survival benefit over Rd in newly diagnosed myeloma. However, it is
an expensive regimen out of reach in many countries due to economic and regulatory issues. Comparative data on less expensive triplets such as VCD or VTD that can be used in place of VRD are not available (Figure 2A). The absence of such data does not automatically indicate these regimens are inferior to VRD. In fact, for purposes of initial therapy, they may have similar activity, and would be reasonable alternatives to VRD for the treatment of newly diagnosed multiple myeloma.

Similarly, data are limited on the duration of posttransplant lenalidomide maintenance in myeloma. Randomized studies show that lenalidomide significantly prolongs progression-free survival; overall survival results are less clear and the optimal duration of maintenance is unknown. In our opinion, it might be cost-effective to administer lenalidomide for a limited duration of time (1-2 years). There are many limitations to the randomized trials of lenalidomide maintenance to determine appropriate duration of therapy, and outcome appears excellent in a recent randomized trial that administered maintenance for 1 year. Thus, if the costs of indefinite maintenance are prohibitive and not possible in clinical practice, an approach of limited duration of therapy is a reasonable alternative to not administering any posttransplant treatment.

In relapsed myeloma, where newer drugs are either unaffordable or unavailable, it is still possible to deliver effective salvage therapy and keep the disease in control for many years. This includes use of less expensive combinations such as VCD, VTD, or a second ASCT. Among the new regimens, using DRD may provide the most prolonged duration of remission and may be more cost-effective in the long run (Figure 2B). There are no data that the sequence in which regimens are administered matters in terms of overall survival. Thus, using less expensive regimens early in the disease course would be more cost-effective because the duration of therapy decreases with each relapse. Furthermore, over time, the cost of regimens may decrease as some drugs go off patent and generics emerge, or competitors with the same mechanism of action emerge putting price pressure.

We recognize these are less than ideal stop-gap recommendations. The IMWG is in the process of analyzing available data and is developing guidelines and pathways that take cost into account. We strongly feel that as drugs become generic, we should demand greater standards of evidence in order for more expensive brand-name versions to be adopted. For example, as bortezomib becomes generic, there are little data from well-executed trials that administering a more expensive proteasome inhibitor first will produce better survival. We should demand such data rather than small trials that purportedly show improvement in surrogate end points.

**Strategies for value-oriented clinical trials**

We need to focus our clinical trial efforts on identifying ways in which to provide the most cost-effective care and those that address strategic questions. When designing a clinical trial comparing 2 therapeutic strategies, investigators should address the question of efficiency (cost-effectiveness) as secondary objective. A recent paper has outlined several high-priority trials that need to be conducted in myeloma to determine treatment approaches that provide the best value.
types of trials are seldom pursued by pharmaceutical companies and need significant funding. We understand that due to the rapid pace of advances many recent randomized trials have been conducted primarily for regulatory approval of new drugs. These are valuable in terms of making new treatments available, but are clearly not designed to provide answers to strategic questions.

First, we need trials that can identify drugs that work well in each subtype, but more importantly from a cost standpoint we also need trials that can identify drugs that are unlikely to work in a given cytogenetic subtype. Second, we need to determine whether an equivalent degree of survival benefit can be obtained with a short course of therapy (similar to that used in diffuse large cell lymphoma) compared with the current approach prolonged therapy for many years. We already know that ~15% of patients with newly diagnosed myeloma can do extraordinarily well for a prolonged period of time with just Rd or Rd plus ASCT. It is likely that with some modern combinations we can identify a subset of patients who can do well for many years following ~1 year of initial therapy. The point is that we will never find out the answer if we do not embark on trials testing this approach. Third, we need to determine whether we can adjust therapy based on response, so that patients who have achieved an minimal residual disease–negative state can safely stop therapy, thereby providing improved value and quality of life.

Clearly, these are exciting times for myeloma, and the hopes of our patients for long-term survival and possible cure depend on our ability to translate current advances into realistic treatments that can be delivered to patients worldwide. The major barrier is economic, and we should do everything we can to make affordable care for myeloma happen, by providing solutions to lower cost of life-saving drugs, by adapting treatment pathways that provide the most cost-effective care in our practice, and through cleverly designed clinical trials.

Acknowledgments

This work was supported in part by grants CA 107476, CA 108762, and CA186781 from the National Institutes of Health, National Cancer Institute, Rockville, MD.

Authorship

Contribution: S.V.R. and J.L.H. conceived of the paper, researched the literature, and wrote the manuscript.

Conflict-of-interest disclosure: J.L.H. has served on a “think-tank” sponsored by Janssen. S.V.R. declares no competing financial interests.

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