

Economic and Clinical Impact of Multiple Myeloma to Managed Care

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ABSTRACT

BACKGROUND: Because of the development of novel agents such as immunomodulators, proteasome inhibitors, and bisphosphonates, the standards of care for the multiple myeloma (MM) patient have changed. The costs associated with current and emerging therapies, as well as supportive care, are significant and pose a tremendous financial burden to both patients and managed care.

OBJECTIVE: To review the economic impact of MM and to weigh the advantages and disadvantages of current treatments in bringing value for prolonged life versus the cost of treatment. This chapter will also discuss the need for thorough data review and pharmacoeconomic analyses to determine the most cost-effective therapies.

SUMMARY: Although MM accounts for only a small percentage of all cancer types, the costs associated with treating and managing it are among the highest. Recent developments in diagnosing, treating, and managing myeloma have led to novel treatment strategies. Immunomodulators, proteasome inhibitors, and bisphosphonates are improving response rates and preserving quality of life. However, these agents are not replacing older treatment modalities, but being used in addition to them. Intensive chemotherapy, stem cell transplantation, and supportive care are all important components in achieving treatment goals.

Costs associated with stem cell transplants and complications of the disease add to the economic burden of myeloma. Additional costs for routine diagnostics to measure the progression of the disease or response to treatment need to be considered. Complications (e.g., lytic bone disease, infection, anemia, and renal failure) also add to morbidity and mortality, thus increasing the burden to the patient and the health care system as a whole.

Financial and time constraints of caregivers must also be considered, as well as the added administrative burdens to health care providers.

CONCLUSION: New standards of care in the treatment and management of myeloma are likely to lead to significant increases in costs. Although costs are not the only elements to be considered, they are crucial in the management of this already costly disease. All aspects of myeloma treatment and supportive care must be evaluated and analyzed. Cost of pharmaceuticals alone must not be a driving factor in treatment decisions. Economic analyses can be used to demonstrate that the least expensive alternative is not always the most economical, and that it may not produce an optimal outcome for both the health plan and the patient. Although cost containment is clearly an important objective, quality of care is the first priority, and managed care organizations have the challenge of making balanced cost and benefit assessments.

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Impact of Changing the Standard of Care in Multiple Myeloma

More than 10 million Americans currently live with cancer, either active or in remission. The financial costs of cancer treatment are a burden to the patients diagnosed with cancer, their families, their employers, managed care providers, and society as a whole. Cancer treatment (for all types of cancer) accounted for an estimated \$72.1 billion in 2004. That was about 5% of spending for all medical treatment in the United States. Between 1995 and 2004, the overall costs of treating cancer increased by 75%, and cancer costs are expected to increase at a faster rate than overall medical expenditures in the future.^{1,2} The NIH estimated the overall costs for cancer in 2007 to be \$219.2 billion: \$89 billion in direct medical expenses, \$18.2 billion in indirect morbidity, and \$112 billion in indirect mortality.³ Cancer cases are expected to increase, relative to other disease categories, as the population ages.¹ The number of individuals aged 65 years or older was observed at 35 million in the 2000 Census and is expected to increase to 80 million by 2040.² With improvements in outcomes, a larger portion of these patients with cancer are achieving remission, which increases the number of patients undergoing treatment and monitoring at any given time. Some forms of cancer have already become chronic rather than acute diseases.

Although multiple myeloma (MM) accounts for only a small percentage (about 1%) of all cancers, the costs associated with myeloma are among the highest. Of the 1,437,180 estimated number of new cancer cases projected for 2008, approximately 19,920 individuals will be diagnosed with MM.⁴ The median age at diagnosis is 70 years, and myeloma occurs in men (7 per 100,000) at a rate 56% higher than women (4.5 per 100,000). The highest incidence rate occurs in African Americans, especially black men aged 80-84 years and older.⁵ There has been a significant improvement in overall 5-year survival in patients with MM since the 1960s: 12% from 1960 to 1963 for whites to 34% from 1996 to 2003 for all races. Approximately 10,790 deaths from myeloma are anticipated this year.⁵

Recent discoveries in the genetic abnormalities associated with MM and better understanding of the bone marrow microenvironment have led to new diagnostic, prognostic, and treatment strategies. The development of new agents such as immunomodulators, proteasome inhibitors, and bisphosphonates are improving response rates, preserving quality of life, and controlling disease activity. At this point, these new agents are not replacing old treatment modalities. For example, many patients will undergo intensive chemotherapy as well as stem cell transplant, and require supportive care. All of these factors add to the overall cost of treating the patient with MM, yet they are all very important components in achieving the goals of treatment. To date, no studies or models have been done that analyze the cost associated with all aspects involved with treating the patient with MM.

With the recent publication of the National Comprehensive Cancer Network (NCCN) guidelines for MM, it is possible to consider that there may be opportunities to consider cost implications of the various therapies. For example, when considering immunomodulators, both lenalidomide and thalidomide combination therapies are available among the 8 primary induction therapies, creating an opportunity for health plans to prefer 1 agent over the other; thalidomide regimens carry 2A-level evidence, whereas lenalidomide is considered 2B-level evidence. At the substantially lower cost for thalidomide, and no comparative studies of these 2 agents, plans may consider 1 agent preferred.⁶ NCCN categories are defined in the table in the previous article by Schwartz and Vozniak in this *JMCP* supplement.

However, decisions about the course of therapy must be tailored to each individual patient based on the results of their physical examination, laboratory tests, age, general health state, symptoms, complications, previous treatments, lifestyle, and views on quality of life. Asymptomatic patients are usually only treated with supportive care, although they require regular monitoring and testing. Symptomatic, or active, myeloma is more complicated and requires more clinical and economic consideration. In patients with active MM, treatment decisions are based on candidacy for stem cell transplant and high-dose chemotherapy.⁷

Patients with active, symptomatic myeloma should begin treatment as soon as possible for the best outcome. Determining which regimen is best for each patient is the challenge. We now know that over- and underexpressed genes are associated with disease progression, drug resistance, and prognosis.⁸ Although gene expression profiling and array comparative genomic hybridization are still experimental, they may replace or be used in addition to previous technology such as fluorescence in situ hybridization analysis or gene sequencing to better define high-risk patients in the future.⁸ With more specific genetic tests, we will be able to predict prognosis based on genetic abnormalities and develop a strategy for treatment (e.g., treat patients with poorer prognoses more aggressively).

Patients who are not candidates for stem cell transplant often receive alkylating agents (such as melphalan) and corticosteroids (such as prednisone). This regimen is fairly inexpensive, comparatively, costing an estimated \$10,000 per patient on a lifetime basis.⁷ Other combinations including melphalan/prednisone/thalidomide; melphalan/prednisone/bortezomib; vincristine/doxorubicin/dexamethasone; dexamethasone; thalidomide/dexamethasone (thal-dex); and liposomal doxorubicin/vincristine/dexamethasone are also commonly used.⁶ Nontransplant patients are typically treated with initial therapy for about 12 months or until their response to therapy has leveled off. After that, patients usually receive some form of maintenance therapy and supportive care.⁷

Pegylated liposomal doxorubicin (or liposomal doxorubicin) offers reduced toxicity, compared with conventional doxorubicin. However, it comes with a higher price tag when looking

at acquisition costs alone. One study comparing liposomal doxorubicin, vincristine, and low-dose dexamethasone (DVd) versus conventional doxorubicin, vincristine, and low-dose dexamethasone (VAd) showed significantly higher drug costs in the liposomal doxorubicin (DVd) arm. However, lower costs for drug administration and supportive care more than offset this difference, resulting in nominally lower overall study drug treatment costs for the DVd arm (DVd, \$34,442; VAd, \$35,846; $P=0.76$). The DVd regimen demonstrated similar efficacy with less toxicity and supportive care than the VAd regimen, which may improve clinical utility and optimize the opportunity for transplantation.⁹

Initial therapy for stem cell transplant candidates includes induction therapy prior to transplant.⁶ Three or 4 cycles of induction therapy to minimize tumor burden are followed by stem cell collection, or harvest, for use in transplant. The cost of autologous stem cell transplant has been estimated at \$20,000-\$60,000. However, it remains the standard of therapy to achieve remission in myeloma patients. A second transplant may be necessary for patients who do not achieve complete remission after the first stem cell transplant.⁷

A retrospective study of 8,891 patients with MM and lymphoma admitted to U.S. hospitals for hematopoietic stem cell transplant (HSCT) over a 2-year period (2000-2001) was extracted from the Nationwide Inpatient Sample (NIS).¹⁰ Mean hospital charges were examined and transformed into cost by using Medicare cost-to-charge ratios. Results showed the mean hospital cost of HSCT during this period was \$51,312. In more than half of admissions, infectious complications and stomatitis were the most frequent (approximately 60% and 40%, respectively), and were associated with increased hospital costs, ranging from \$15,000 to \$50,000. Hospitalization resulting in death predicted a 14.6-day increase in the duration of inpatient admission and an increase in the mean hospital cost of 31% (approximately \$84,300). The higher mean costs were a function of longer length of stay and greater resource intensity. Whereas the absence of adverse events was associated with a decreased length of stay (4.7 days; $P=0.012$), resulting in predicted hospital costs nearly 20% below the cohort average. The results of this study show that interventions, particularly those targeted to reduce the risk of infection, could contribute significantly to reducing the morbidity of HSCT, as well as its cost.¹⁰

Financial and time constraints of caregivers for stem cell transplant patients should also be taken into account. Recently, a prospective evaluation of the time commitment and financial requirements of caregivers of autologous stem cell recipients during the period of inpatient hospitalization (median length of stay was 22 days) was performed. Caregivers lost hours from work and had significant out-of-pocket expenses for accommodations, gasoline, and food. The median caregiver travel time and distance was 17.8 hours and 829 miles, respectively. The median out-of-pocket caregiver expenses were \$849 (caregivers who used

TABLE 1 Budget Impact Model Comparing Resource Use of Four Approved Therapies for Myeloma in the United States^a

Therapy Arm	Bortezomib	Bortezomib/ Dexamethasone	Lenalid/e/ Dexamethasone	Thalidomide/ Dexamethasone
Drug costs	\$22,734	\$34,794	\$64,806	\$37,281
Medical costs	\$5,886	\$6,882	\$1,623	\$1,397
Adverse event costs	\$5,209	\$6,116	\$5,243	\$7,910
Total cost per patient	\$33,289	\$47,792	\$71,672	\$46,588
Type of prophylaxis	Herpes Zoster	Herpes Zoster	DVT/PE	DVT/PE
Total cost with prophylaxis per patient	\$33,966	\$47,929	\$72,822	\$47,002

^aFullerton DS, Hulehatt H, Huang H., et al. ASH 2007 Annual Meeting, Atlanta, GA, Dec 8–11, 2007 [Abstract No. 3324].

This model assumes the following methods: (1) Direct costs are for 1 cycle of treatment with drug costs from the 2007 Red Book, (2) duration of therapy was based on published median duration therapy protocols and dosages, and (3) assumptions of recommended prophylaxis for herpes zoster and DVT/PE are based on NCCN guidelines. AE = adverse event; DVT = deep vein thrombosis; PE = pulmonary embolism.

local accommodations) versus \$181 (caregivers who stayed in the hospital room). The results of this study demonstrate that there is a significant financial and time requirement on the part of the caregiver when a family member or significant other is hospitalized for stem cell transplantation.¹¹

Acquisition costs of immunomodulatory agents and proteasome inhibitors are substantial. Based on 85% of Average Wholesale Price (AWP) from January and April of 2007, acquisition costs of lenalidomide and thalidomide are \$78,183 and \$53,295, respectively, per year per patient.⁶ Because of suggestions of increased survival rates associated with these agents, this increased cost may be considered to be warranted. But, without studies comparing thal-dex with lenalid-dex, true comparative outcomes cannot be assessed.¹² Although more cost analyses and outcome studies must be performed, increased survival rates and longer remission periods appear promising in these newer, novel agents. Bortezomib is associated with a lower annual cost of \$27,120 per patient per year based on 85% of AWP from January 2007.⁷

Additional economic considerations should also be taken into account when determining a treatment plan for the patient with MM. Is the patient on Medicare, Medicaid, or privately insured? Fifty percent of MM patients are older than 71 years of age; so Medicare coverage must be considered. Medicare Part D covers oral agents, whereas Medicare Part B covers injectable agents provided by a physician. Also, Medicare and Medicaid coverage varies from state to state and changes yearly. Injectable bortezomib carries an acquisition cost of about \$27,120 per year per patient;⁷ yet if that patient has Medicare Part B and secondary insurance (88% of Medicare Part B beneficiaries do have secondary insurance), he or she may end up with little or no out-of-pocket expense for that drug. However, if the patient is treated with oral lenalidomide (\$78,183 per year),⁷ Medicare Part D would cover only a percentage, leaving the patient to pay around \$7,500

out of pocket. Notable cost differences such as these have a considerable impact on prescribing, particularly when the efficacy of the agents in question appears to be similar.¹³

Administrative burdens also need to be considered. The immunomodulatory drugs thalidomide and lenalidomide are available only under restricted distribution programs. Significant staff time may be required to access these types of distribution systems, with no reimbursement provided to the practice. All of the facets around injections must also be considered, including the use of the infusion center and the staff hours required to administer injections.¹³ However, there is debate around this, resulting in the need for economic analysis between oral and injectable therapies.

An example of a study showing these types of comparisons between orals and injectables was conducted by Fullerton et al., in which they compared 4 approved therapies for MM in the United States. Direct medical costs were compared using 1 therapeutic course of bortezomib, bortezomib/doxil, thalidomide/low-dose dexamethasone, and lenalidomide/low-dose dexamethasone for MM. Anticipated complications for herpes zoster and deep vein thrombosis (DVT)/pulmonary embolism were also assumed in the model. Other adverse events included neutropenia (bortezomib/dexamethasone and lenalid/dex), thrombocytopenia (both thalidomide regimens), peripheral neuropathy (thal/dex), and a higher rate of VTE (lenalid/dex and thal/dex). The impact model showed that drug costs were the major driver of direct medical costs and represented a large difference in resource use among the therapies used.¹⁴ (Table 1)

Other considerations for costs should be the type of diagnostic testing used to record disease progression. Skeletal surveys, MRI, and positron emission tomography (PET) scans may be performed to determine level of disease progression as well as response to treatment. Although PET scans are much more expensive than skeletal surveys, they show where lesions are in

TABLE 2 Estimated Number of Cases with Cancer and MBD in the United States in 2004 by Payer^a

Cancer Type	Prevalence Cancer, MBD, All Payers			Prevalence MBD By Payer		
	Cancer Cases	MBD Cases	MBD Rate	Commercial	Medicare	Other ^b
Breast	939,192	69,858	7.4%	30,791	25,307	13,761
Prostate	735,812	47,607	6.5%	10,010	32,553	5,044
Lung	237,469	37,002	15.6%	10,149	21,740	5,113
Multiple Myeloma	51,380	14,781	28.8%	4,591	7,877	2,313
Other	2,898,134	86,888	3.0%	29,928	40,073	16,887
Totals	4,861,987	256,137	5.3%	85,469	127,550	43,118

^aSchulman KL, Kohles J. *Cancer*. 2007;109:2334–42.

^bIncludes Champus, Medicaid, Uninsured Patients.

MBD = metastatic bone disease.

the body and whether those lesions are responding to treatment often more quickly than traditional diagnostics.

Supportive Care Issues

Anemia and bone disease are the principal causes of morbidity, whereas infections and renal failure are the main causes of mortality in MM patients.¹⁵

Anemia

Because anemia is present in two thirds of myeloma patients at diagnosis, direct costs associated with transfusions, laboratory tests, and treatment of anemia must be accounted for, as well as the indirect costs of decreased quality of life and absenteeism caused by fatigue. Treatment of anemia often consists of erythropoietin administration, adding another costly piece to the puzzle.¹⁵

Bone Lesions

The national cost burden for patients with metastatic bone disease (MBD) in 2004 dollars was estimated at \$12.6 billion in total direct medical cost. In a recent study, 5.3% of U.S. patients with cancer were projected to have MBD. Of that 5.3%, 28.8% were MM patients as seen in Table 2.² Figures 1 and 2 show incremental expenditure associated with MBD both in commercially insured patients and those with Medicare. The results are from a study of anonymous, patient-level data on health care utilization and cost obtained from the Thomson Medstat MarketScan Research Database. The end result suggests that MBD is a significant driver of overall oncology cost.²

Intravenous bisphosphonates delay and reduce the number of skeletal events and reduce bone pain in MM patients. Current NCCN guidelines recommend that all patients with documented bone disease, including osteopenia, receive bisphosphonate therapy.⁶ Although additional studies are needed to clarify conflicting data from current studies, most studies show no significant

cost differences between patients receiving zoledronic acid or pamidronate. Studies also show no difference in the incidence of skeletal-related events when comparing zoledronic acid 4 mg with pamidronate 90 mg every 3-4 weeks for up to 25 months.^{16,17} Oral bisphosphonates offer greater convenience and reduced costs. However, results from clinical trials have been mixed.^{6,18-20}

In Ontario, Canada, the Hamilton Regional Cancer Center offered patients receiving the bisphosphonate pamidronate 2 treatment options.²¹ One cohort completed treatment at the clinic using traditional intravenous therapy. The second cohort had treatment initiated at the clinic but completed at home. Data were collected for 1 year (1997-1998). Home therapy was completed by 48 patients, accounting for 299 cycles. The incremental cost of the infusion device and training was \$5.50 per cycle, or \$4,636, in Canadian dollars, for the 299 cycles, compared with \$68.49 per cycle, or \$20,477, in Canadian dollars for treatment completed in the clinic. The results demonstrated that clinic overheads, the cost of a portable and disposable infusion device, and the cost of lost work and leisure time had a great impact on incremental costs. Shifting treatment from the clinic to the home resulted in net cost savings to society.²¹

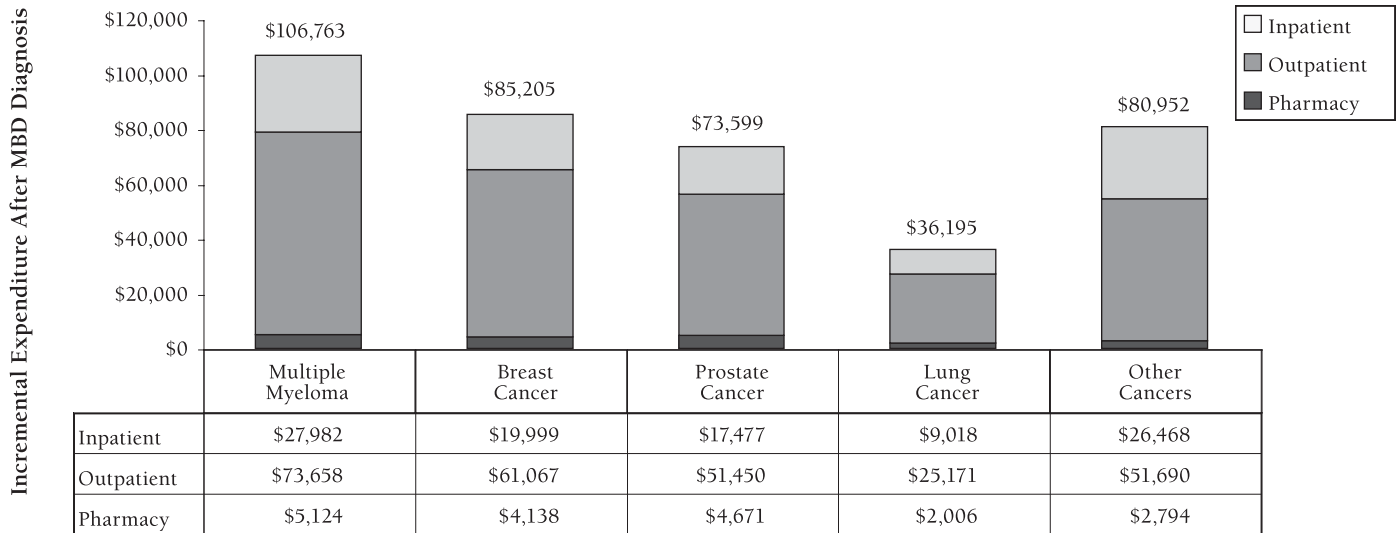
In a 2007 study, 3,049 patients with cancer were evaluated for pathologic fractures. Cancer types included MM (n=513), breast (n=1130), prostate (n=640), or lung or other solid tumors (n=766). Patients with MM had the highest fracture incidence (43%). In all tumor types except lung, pathologic fracture was associated with a significant increase in risk of death. Patients with MM who developed a pathological fracture had a greater than 20% increased risk of death.²²

Deep Vein Thrombosis and Venous Thromboembolism

DVT and venous thromboembolism (VTE) are risks in all patients with cancer.²³ VTE in patients with cancer recurs 3 times more often than in patients who do not have cancer and requires

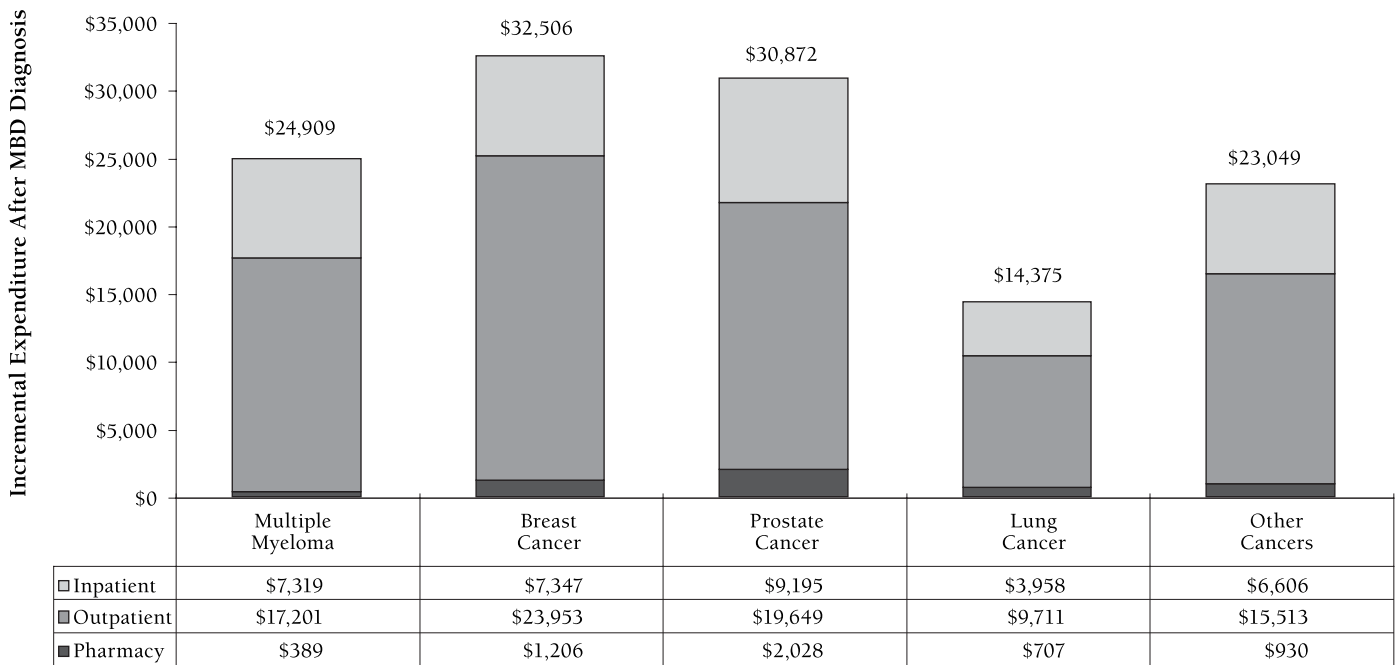
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FIGURE 1 Private Payer Costs of MBD: All Cancers^a



^aSchulman KL, Kohles J. *Cancer*. 2007;109:2334-42.²

FIGURE 2 Medicare Costs of MBD: All Cancers^a



^aSchulman KL, Kohles J. *Cancer*. 2007;109:2334-42.²

long-term treatment with anticoagulants with a 2-fold greater risk of bleeding complications than patients without cancer. VTE also consumes health care resources. In a retrospective analysis, the mean length of DVT-attributable hospitalization was 11 days, and the average cost of hospitalization for the index DVT episode was \$20,065 in 2002 U.S. dollars. Reducing VTE in patients with cancer would have a significant impact on morbidity, outcomes, use of health care resources, and, above all, mortality.²³

Renal Complications

Dialysis and supportive care associated with end-stage renal disease also add to the cumulative costs of treating the patient with MM. Plasma exchange is effective in removing the monoclonal light chains responsible for renal failure and may restore normal renal function in more than half of patients. Aggressively treating the myeloma often leads to recovery of renal function and has been shown to improve overall survival in most studies.¹⁵

Infections

Infections are a primary cause of death in patients with MM, and the risk increases during induction chemotherapy, after stem cell transplant, and during long-term maintenance with steroids. A randomized, controlled study showed that intravenous immunoglobulin prophylaxis protected against life-threatening infections and reduced the risk of recurrent infections.¹⁴ Preventing infection will lead to decreased hospitalizations, morbidity, and mortality.¹⁰

Conclusion

As new, more advanced, and more expensive treatments are adopted as standards of care, costs are also likely to increase significantly.¹ Economic factors need to be considered in the delivery of care. Although they are not the only elements to be considered, they are crucial in the management of an already costly disease. There is a definite need for thorough data review and pharmacoeconomic analyses to determine the most cost-effective therapies, especially with the introduction of newer, potentially more efficacious agents.⁷

After completion of a Health Insurance Portability and Accountability Act form, Nationwide Inpatient Sample data are publicly available on their Web site, which substantially reduces data acquisition costs. These data are updated annually and permit analyses of secular trends in application to technology, outcome, and cost. Linking to other publicly available databases, such as the American Hospital Association database, could be further used to investigate the influence of provider and center characteristics. This information is useful both to payers and policy makers, and can also be used for hypothesis generation, identifying questions for which more specific primary and/or prospective data collection would be appropriate.¹⁰

Pharmacoeconomic analyses and head-to-head trials between the newer immunomodulatory agents and proteasome inhibitors

will assist clinicians and managed care organizations in determining the cost-effectiveness and survival benefit of each agent.⁷ Fast-paced changes in health care have heightened awareness of the costs of new therapies. Although cost containment is an important objective, quality of care is the first priority. Economic analyses can be used to demonstrate that the least expensive alternative is not always the most economical, and that it may not produce an optimal outcome both for the patient and the health plan.²⁴ It is shortsighted to look at pharmaceuticals only in terms of their costs. The task is to make a balanced assessment of costs and benefits. Evidence suggests that, when properly chosen and managed, pharmaceuticals yield benefits that more than justify their costs—in fact, they add value.²⁵ More studies still need to be done to determine outcomes for patients with MM, including overall survival, length of remission, decrease in pain and symptoms, and improvement in quality of life.

A partnership among patients, providers, and managed care organizations in which information sharing and open communication is the norm is necessary if the treatment of MM is to be addressed effectively and in a timely manner. This relationship, coupled with pharmacoeconomic analysis for emerging comparison data, will ensure cost-effective, outcomes-based treatment of MM in managed care.⁷

DISCLOSURES

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