Many Shades of Disparities in Myeloma Care

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Overview

Treatment of multiple myeloma (MM) has notably evolved with improved patient outcomes over the past few years. Several new drugs have become available, and large national and international clinical trials have set the stage for evidence-based medicine guidelines for the treatment of patients with MM. Although patient outcomes have undoubtedly improved, data increasingly show that several disparities exist at varying levels of health care and that these disparities make the care of patients heterogenous and potentially result in inferior outcomes. These disparities have been described with regard to patient age, race/ethnicity, rural-urban residence, socioeconomic status, and insurance type, among other factors. Looking at the global picture of MM care, there is substantial variation among different countries, primarily depending on the disparate availability of anti-MM drugs and access to quality health care across the world, limiting the delivery of innovative therapeutic approaches at the individual patient level. The causes of these national and international disparities could be multifactorial, intricate, and difficult to isolate. Yet the ongoing research in this field is encouraging, and there seems to be growing momentum to understand such disparities and their causes. It is hoped that this research will lead to solutions that can be implemented in the near future. This review focuses on certain aspects of disparities in MM care, highlighting disparities among different racial/ethnic subgroups, rural-urban differences in America, and global disparities at an international level.

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States, with an estimated more than 30,000 new cases diagnosed in 2018.[1] An estimate of cancer diagnoses across 185 countries reports approximately 160,000 new myeloma cases diagnosed in 2018 globally.[2] Management of MM has evolved considerably over the past decade, resulting in a substantial improvement in patient outcomes and a reported 5-year relative survival rate (RSR) of 50.7% in the United States, which has been steadily improving based on national database estimates.[1] This improvement in survival is seen in other high-income countries as well; for instance, the 5-year RSR for MM in Sweden increased from 28% in 1973 to 1982 to 41% in 2003 to 2013.[3] Improved outcomes have been attributed to considerable advances in patient treatment, better understanding of the disease biology, development of new therapies, and improved supportive care measures.[4,5] With the ever-changing therapeutic landscape and a constant update of clinical trial and real-world evidence, MM care has become increasingly complex with widespread variability. In an ideal case, we would expect all patients with MM to receive the most evidence-based and standard treatment, resulting in a universal improvement in outcomes. Although there are data to support that outcomes of MM have improved overall, disparities in the care of patients with MM have been described extensively in the United States as well as globally. The timing and choice of care may not be optimal for patients of certain demographics, such as racial/ethnic subgroups, rural regions, areas of low socioeconomic status, and elderly populations in the United States.[5,6] Indeed, patients of racial/ethnic minorities and those living in rural America are shown to have inferior outcomes for certain cancers, including MM.[5-8] Similarly, reports show that age-adjusted deaths from MM have been increasing in low- and middle-income countries across the world.[9] Although the specifics may be somewhat different in various clinical and geographic settings, it seems that a key driver of this disparity in the United States and internationally is the difference in access to and delivery of high-quality MM care.[5,6,9,10] With an increasing incidence and prevalence of MM, understanding these disparities and their potential causes and attempting to mitigate them becomes an urgent need.

This review will focus on selected aspects of disparities in MM care, highlighting our current knowledge of racial/ethnic, rural-urban, and global factors (Fig. 1).

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RACIAL/ETHNIC DISPARITIES

Race/Ethnicity and Disease Characteristics

The treatment of MM has evolved such that there is an attempt to tailor the therapy to an individual patient by considering the patient's MM genotypic risk category, clinical features (including myeloma-defining events), and comorbidities, among other factors.[11-13] Previous studies suggested that the disease biology and

PRACTICAL APPLICATIONS

- Despite therapeutic advancements, disparities in multiple myeloma care exist at several levels affecting optimal patient care and outcomes.
- Racial/ethnic disparities in myeloma care are multifactorial with differential utilization of and access to treatments, such as novel drugs and stem cell transplantation, along with the interplay of factors, such as patient age and insurance status.
- Patients living in rural America have disparate access to quality health care, including delay in seeking treatments, delay in timely referral for stem cell transplantation, and less participation in clinical trials, than their counterparts living in urban areas.
- Globally, there are stark differences in myeloma care, with worse outcomes in low- and middle-income countries as a result of limited access to novel drugs, stem cell transplantation, and specialized health care professionals, requiring tailored evidence-based guidelines to be developed depending on resource availability.
- Recent data suggest that, if guideline-based myeloma care is provided, outcomes across distinct patient strata turn out to be similar, which further suggests that access to optimal health care may be a crucial factor contributing to disparities.

characteristics may be different among patients with MM from different racial and ethnic groups.[5,14-17] African American patients are thought to have a lower incidence of certain high-risk genomic profiles for MM, including certain translocations involving chromosome 14 and deletion of 17p, an extremely high-risk feature in MM.[15,17] This is considered to be one explanation for improved outcomes in African American patients despite evidence that they have lower access to some of the novel therapies for MM, including stem cell transplantation (SCT).[5,18,19] Yet such reports of genomic differences between racial groups are far from being definitive and surely must be replicated in mutually exclusive databases with ample racial/ethnic minority representation to confirm their validity. Similarly, the incidence of myeloma-defining events, myeloma-related end-organ damage (e.g., need for kidney dialysis), and bone fractures has been reported, with varying incidence among racial/ethnic subgroups.[5,16] These factors can dictate the timing and choice of therapy and, in some cases, whether aggressive therapy, including multiagent regimens and SCT, is offered to patients.

Race/Ethnicity and Patient Age

Disease incidence, access to care, and outcomes have been evaluated in relation to patient race/ethnicity in multiple settings across health care. Age and certain age-associated comorbidities have been reported as independent prognostic markers in outcomes of patients with MM.[18] Although there is a substantial body of literature showing that African American patients have a younger age at onset for MM compared with white patients, there are some reports that Hispanic populations may have the youngest age at onset of all racial/ethnic subgroups.[18-21] There could be an interplay between this observation and insurance type, occupation status, treatment received, and patient outcomes. Indeed, an analysis of survival gain by age and race/ethnicity strata showed that, although there were notable gains in the 10-year RSR for patients with MM younger than age 65 for all racial/ethnic subgroups, there was no substantial improvement in the 10-year RSR for African American patients age 65 to 74 at the time of MM diagnosis. This shows an interaction between age and ethnicity in terms of utilization of SCT, such that older African American patients are less likely than older white patients with MM to undergo SCT.[5,22]

Race/Ethnicity and Access to MM Care

As mentioned above, African American patients were reported to have a better outcome than white patients in several prior population-based studies.[18,19] The earliest of these studies to report a better median overall survival (OS) for African American patients showed that, although the RSR increased significantly over time from 1973 to 2005 in white patients, there was a smaller, nonsignificant change in the RSR for African American patients over the same time period.[19] This suggests a growing disparity over time, possibly because of unequal access and/or response to novel therapeutic strategies. In a Center for International Blood and Marrow Transplant Research analysis spanning 1995 to 2005, the 5-year OS and progression-free survival of patients with MM was not substantially different across races despite notable differences in clinical and demographic features.[23] This shows that, when minority patients are provided access to evidence-based myeloma therapeutic options such as SCT, the outcomes of African American patients are at least similar to those for white patients.[16,24] This result also raises the discussion of whether outcomes in minorities, including African American populations, could possibly be further improved if their access to novel therapeutic agents and SCT is less disparate.

Over the years, several studies have highlighted differential utilization of SCT among white patients and racial/ethnic minorities. A study with data from 1997 to 2002 from the Surveillance, Epidemiology, and End Results Program, the

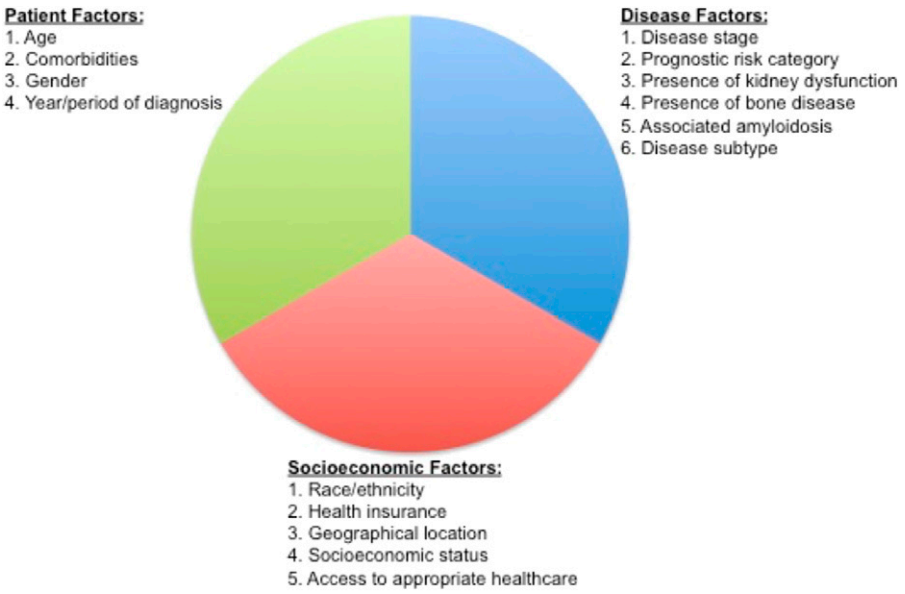

FIGURE 1. Selected Factors That May Affect Access to Treatment and Outcomes for Patients With Multiple Myeloma

Center for International Blood and Marrow Transplant Research, and the U.S. Census explored SCT utilization for hematologic malignancies, including MM, by patient race/ethnicity and sex.[25] The age-adjusted odds of receiving SCT for MM were significantly higher for white than for African American patients (odds ratio, 1.75; 95% CI, 1.64–1.86; $p < .01$). Others reported similar results, with African American patients less likely to receive SCT compared with white patients, even after controlling for age, sex, socioeconomic status, insurance provider, and comorbidity score.[26] Certainly, there could be other nonmedical barriers to early access to SCT (e.g., social and cultural beliefs, lack of a support system, inability to obtain a prolonged time duration away from work, or family responsibilities secondary to the socioeconomic status). These have not been adequately addressed, because a lot of these factors are not available in population-based data. These factors may be addressed better in single- or multi-institution prospective cohorts or in specifically designed studies better suited to their exploration.

Although exploratory analyses for African American and white patients have been reported on several occasions, more recent studies have started evaluating treatment utilization trends among the Hispanic population, the fastest-growing racial/ethnic subgroup in the United States, as well. These analyses show that Hispanic patients have a significantly lower rate of receiving SCT for initial management of MM compared with whites.[27,28] In fact, one recent analysis showed that Hispanic patients have the lowest rate of SCT use of all racial/ethnic subgroups studied in the United States.[22] The optimal timing of SCT in MM care has been a topic of debate, but there seems to be a consensus that patients who are considered transplant eligible should receive this standard-of-care therapeutic modality relatively early in their disease course.[29] A study examining single-center referral patterns documented that African American patients were referred for an SCT significantly later in their disease course than white patients.[30] Providing timely access to evidence-based care across all racial/ethnic groups is imperative, and these data should lead to efforts that mitigate such disparities with certain implications on patient outcomes.

To address the use of novel therapeutic agents, including proteasome inhibitors and immunomodulatory drugs, population-based databases have been frequently used with treatment periods as a surrogate for the type of therapy that a patient with MM might receive. Although survival in MM has improved for all racial/ethnic groups over time, the incremental benefit is shown to be least in minorities (Hispanic patients), suggesting lesser access or response rates to the novel agents compared with non-Hispanic white patients.[18,31] A few recent studies used claims-based data (Surveillance, Epidemiology, and End Results–Medicare) to explore the utilization of specific drugs, including bortezomib, thalidomide, lenalidomide, and, more recently, carfilzomib and pomalidomide, across races/ethnicities (S. Ailawadhi et al, unpublished data, 2019).[5,32,33] One study reported that, over a 3-year period (2007–2009), Hispanic patients had the longest median time to first dose of bortezomib treatment of initial therapy of newly diagnosed MM compared with other racial/ethnic subgroups (median 117 days vs. 46–51 days, $p = .025$). During the first year after MM diagnosis, white and African American patients had higher bortezomib-only usage, whereas Hispanic and Asian patients had higher immunomodulatory drug-only utilization.[32] Furthermore, a substantial increase was seen over years for

lenalidomide and SCT use for all subgroups except Hispanic patients, and a notable increase in bortezomib use was noted for all subgroups except Asian patients.[32] These data suggest that the adoption of clinical trial data and evidence-based guidelines may be different for patients with MM based on race/ethnicity. In another study, investigators examined the same database and reported that, even after controlling for overall health and potential access barriers, African American patients with MM were significantly less likely to undergo SCT and be treated with bortezomib, leading to a potential association with increased hazard of death.[33] It is understandable that the causes of these disparities may be complex, with interplay between several demographic, socioeconomic, and disease-specific characteristics. Isolating specific causes from institutional and/or population-based data can be difficult. Yet, several attempts have been made to better understand these phenomena. One such study looked at the patterns of MM care in the United States and the interplay of patient insurance and race/ethnicity.[34] The investigators reported that, for white patients, there was no statistically significant difference in the use of novel agents for those with Medicare or with private insurance ($p = .2$); for patients of other races/ethnicities, those with Medicare only or Medicaid were significantly less likely to receive novel agents or SCT compared with those with private insurance ($p = .002$). These analyses depict the current therapeutic landscape for various patient subgroups and pave the way to better understand the causes of these disparities and develop potential strategies to overcome them.

Keeping up with the rapid pace of evolution in the field of cancer care can be challenging because of the unprecedented number and fast pace of U.S. Food and Drug Administration approvals of newer agents and unique classes of drugs. Access to evidence-based medicine is considered imperative to translate therapeutic advancements into benefit at an individual patient level. Care at National Cancer Institute–designated comprehensive cancer centers or large-volume tertiary care institutions and participation in clinical trials are considered as such opportunities, administering innovative and leading cancer care with improved patient outcomes.[35,36] In the case of MM, patients who are treated at higher-volume facilities (adjusted for demographic, socioeconomic, geographic, and comorbid factors and year of diagnosis) have been shown to have a lower risk of all-cause mortality compared with patients treated at lower-volume facilities.[37] Yet, for patients with MM, the survival benefit of living in close proximity to National Cancer Institute–designated comprehensive cancer centers was reported to be limited only to whites and was not seen in case of racial/ethnic minorities.[36] Furthermore, clinical trial participation in general, as well as in the case of MM, is very low in the United States, with a significantly lower representation of underprivileged patient subgroups such as racial/ethnic minorities and elderly individuals.[16,38,39] This could represent differences in referral patterns, insurance coverage, sociodemographic factors, or cultural beliefs that determine which patients receive care at certain medical institutions and/or participate in clinical trials.[40]

The data presented here attempt to summarize studies exploring racial/ethnic disparities in MM care. Although we may not yet have specific strategies to overcome these disparities, the amount of work being put into researching this question is encouraging. Finding solutions will indeed require a combination of change in health care delivery strategies, attitudes of patients and clinicians, and institutional and political will along with development of innovative policies.

RURAL-URBAN DISPARITIES

Defining the Problem

Defining rural America can be a difficult task. Various classifications exist, including those from the U.S. Census Bureau[41] and the U.S. Department of Agriculture.[42] Nineteen percent of the U.S. population and a similar percentage of patients with cancer live in rural areas (Fig. 2).[43] Universal access to quality health care remains a challenge in the United States. In an ideal world, patients from rural America should expect the same quality of care as that delivered by experts from a tertiary academic institution. However, this is far from reality, as previous reports have shown.[7] One such report focusing on patients with MM from New Mexico showed a significantly inferior median OS for patients living in rural areas (39 months) compared with patients from urban areas (69 months; $p < .001$).[8] Indeed, disparities such as underutilization of cancer screening tests, lower likelihood of receiving guideline-appropriate therapy, and access to clinical trials exist in association with rural residence.[8,10]

There have been limited studies focusing on patients with MM from rural areas in the United States. One such study from Arkansas reported a higher incidence of MM among patients born and raised in rural areas.[44] In this case-control study over 30 years, farming for more than 10 years was associated with an increased risk for development of MM (odds ratio, 1.87; 95% CI, 1.15–3.16). There appeared to be no notable difference in the median age at diagnosis, sex, or immunophenotype of MM (immunoglobulin G vs. non-immunoglobulin G and light chain only) between rural and urban patients. In this particular study, the rural cohort comprised more white patients with a higher prevalence of tobacco use. Rural patients had a longer duration of initial presenting symptoms prior to MM diagnosis and were more likely to have International Staging System stage III disease,

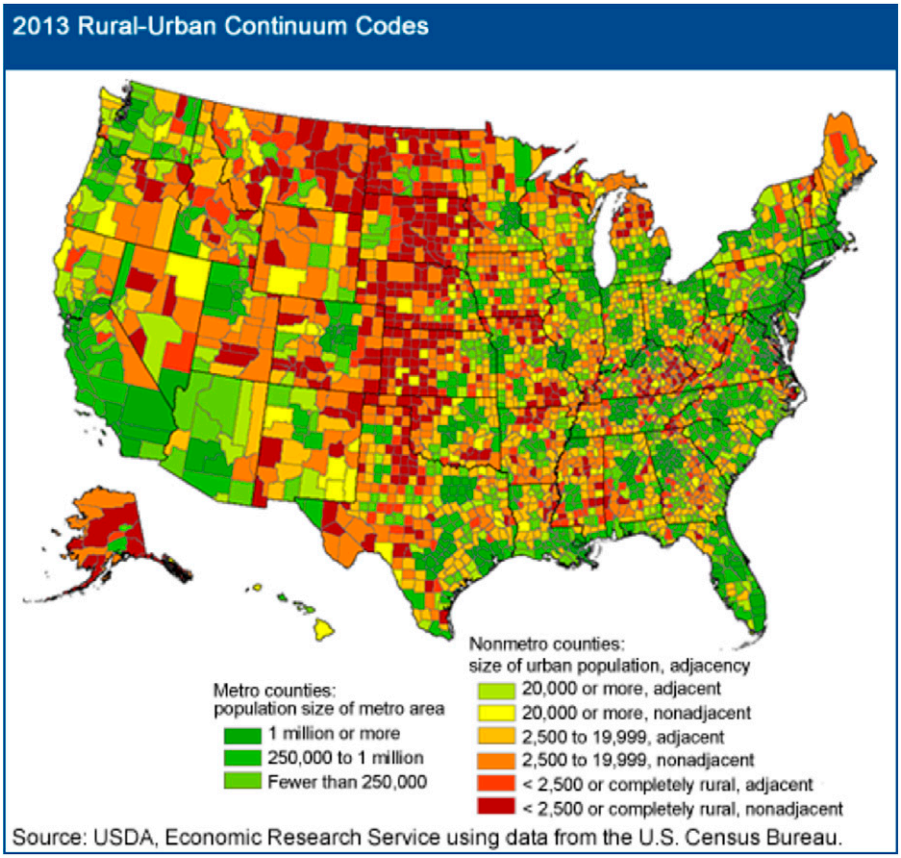

FIGURE 2. Classifying America According to the Rural-Urban Continuum Codes

Adapted from the U.S. Census Bureau.[43]

suggesting that they were more likely to seek medical attention later than their urban counterparts.[44]

Access to MM Care in Rural America

Unlike studies looking at SCT utilization rates among patients with MM of different races and ethnicities, analyses specifically focused on the rural-urban populations are infrequent. In the study from rural New Mexico, one-third of the patients were offered or educated about SCT, but 18.5% received the therapy.[8] There was no difference in transplantation rates between the urban or rural groups, but no comparative outcome analysis was performed based on SCT status. A factor that may affect providing appropriate care to patients is the distance from the treating center. The interplay of patient comorbidities, symptom complex, and complexity of the regimen and treatment schedule could notably affect the patient's ability to travel to the treatment center. Distance could be an important factor for decisions regarding SCT, because patients must travel frequently to the treating institution. Multiple studies have addressed the effect of geographic distance to transplant centers and survival after transplantation. One study found worse survival in rural patients who underwent SCT.[45] This study reported that rural patients had at least a 5% lower probability of survival at 1 year and 5 years after SCT. This study did not comment on the accessibility of SCT to rural patients, but accessibility of the transplant center could be one possible explanation. On the contrary, Lipe et al[46] did not find that distance from the transplant center was associated with worse outcomes for patients with MM.

The lack of health insurance in rural America has been suggested as a contributing factor to worse outcomes for patients with MM.[45] However, the low utilization of SCT may be multifactorial, because a study from a region in Australia with universal free health care coverage failed to show a high acceptance rate of SCT even in this setting where health care coverage would not be a confounding factor.[47]

In a study that combined rural-urban continuum codes and patients' zip codes with the state cancer registry, the investigators found that only 18% of patients with MM in Kansas received SCT between 2011 and 2012, similar to the low SCT rates noted in the United States by others. In a personal survey of 12 hematology-oncology physicians practicing in Kansas and Missouri, we noted that the demographics of patients were not different from any urban cohort, although it appeared that the time from the beginning of symptoms to diagnosis was longer (personal communication, Dr. Siddhartha Ganguly, 2018). In this survey, almost all community oncologists used an evidence-based

triplet regimen for initial therapy of patients with newly diagnosed MM. The referring oncologists also indicated that they referred 50% to 60% of their patients for consideration of SCT to the nearest transplant center, but distance and issues with transportation were the major obstacle to accessing care. The oncologists surveyed agreed that the clinical trial accrual rate was only 0% to 5% among patients from a rural address, which may be even lower than the clinical trial enrollment data mentioned above for the United States (personal communication, Dr. Sue Min Lai, 2018).

A Southwest Oncology Group study showed that the disparity in survival rates between rural and urban patients is minimized when patients are enrolled in clinical trials.[48] This suggests that differences in outcomes of patients from rural America could be pronounced because of inadequate access to quality health care. Although not specific to MM, recent reports have attempted to explore why patients with cancer in rural America may remain underserved.[49] This study identified financial issues on the part of the patient and, relatedly, absence of trained providers in such regions of the country.

Despite growing national awareness of health care inequities, the state of rural Americans diagnosed with cancer has persistently remained inadequate.[49] According to a Centers for Disease Control and Prevention analysis, although overall cancer incidence rates are lower in rural counties, death rates are higher.[50] It seems that the real difference in outcomes of patients with MM depends on the disparity of access to novel therapy, timely referral to a transplant center, and enrollment in clinical trials. Improvement in early diagnosis and staging based on recent guidelines, a close association with a tertiary center, and the availability of clinical trials would certainly go a long way in mitigating the rural versus urban differences. Technology, telemedicine, and social media to increase awareness and grassroots approaches, such as educational seminars for both health care providers and patients from rural areas, should be encouraged as well. In this light, efforts of the National Clinical Trial Outreach and Awareness Initiative, part of the Center for Information and Study for Clinical Research Participation, to improve clinical trial participation are timely and a step in the right direction.

GLOBAL DISPARITIES

Global Burden of MM: Incidence, Prevalence, and Disability-Adjusted Life Years

There are well-recognized ethnic differences in the incidence and prevalence of MM and its precursor state, monoclonal gammopathy of undetermined significance.[19] The incidence of MM (and monoclonal gammopathy of undetermined significance) is two-fold higher among African American compared with white patients.[51] Although the exact incidence of MM in Africa is unknown, the prevalence of monoclonal gammopathy of undetermined significance in Ghana is comparable to the prevalence among African Americans, suggesting a shared ancestry-related genetic susceptibility to plasma cell disorders in black populations.[52] The incidence of MM is lower in Asian populations compared with the United States and other Western countries.[53] Limited data are available on the biologic and genetic factors that may contribute to differences in incidence. A study from the Asian Myeloma Network reported the clinical and biologic characteristics of patients with MM in Asia compared with patients diagnosed in the United States.[54] The median age at diagnosis in Asia was lower (62 vs. 66 years), but the frequency of high-risk cytogenetic abnormalities (detected by fluorescence in situ hybridization) was comparable.[54] Although biologic and genetic factors likely explain some of the observed differences in incidence, lower rates of diagnosis and reporting in low- and middle-income countries as a result of lack of access to cancer diagnostics and care are another important factor.

The best available data on global incidence and mortality come from the comprehensive Global Burden of Disease study, which looked at the global burden of MM over time from 1990 to 2016.[9] Globally, the incidence of MM has increased 125.9%, from 61,307 cases in 1990 to 138,509 cases in 2016. This increase is driven in part by population growth (40.4%) and a global increase in life expectancy (52.9%) and is partly attributable to an increase in the age-specific incidence of MM (32.6%). Although an increase in incidence is seen across all geographic regions, the majority of new patients (72%) are diagnosed in high-income countries.[9] In 2016, nearly 100,000 patients died of MM globally and 38% of the deaths were in low- and middle-income countries. Overall, both age-specific incidence and mortality rates have increased greatly from 1990 to 2016 globally (Fig. 3A and 3B). MM was also responsible for 2.1 million disability-adjusted life years in 2016 globally. This includes both years lost because of premature mortality and years lost as a result of disability.[9]

Global Access to Cancer Care

Access to quality cancer care is a key challenge in most low- and middle-income countries. In a survey of 33 countries in sub-Saharan Africa in 2012 with a total estimated population of 771.2 million, there were only 606 pathologists; this is merely one pathologist per 1.3 million population.[55] Six countries had only one pathologist, whereas one country (Somalia) had no pathologist at all. In comparison, there is one pathologist per 20,638 people in the United States.[55] In 2019, the Directory of Radiotherapy Centers listed a total of 7,390 radiotherapy centers in 148 countries.[56] Of these, the United States had 2,113 centers, and 74 countries had five or fewer radiotherapy centers. A global survey of the clinical oncology workforce published in 2018 included data from

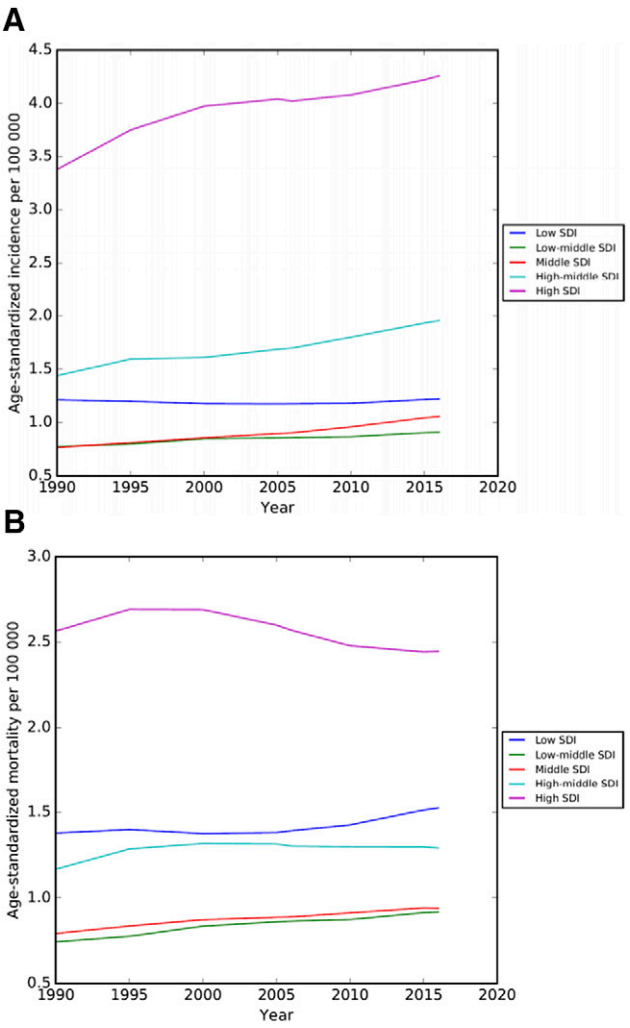

FIGURE 3. Global Trends in Age-Standardized Incidence (A) and Mortality Rates (B) by Sociodemographic Index Between 1990 and 2016
Abbreviation: SDI, sociodemographic index.
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93 countries.[57] Eight countries had no trained oncologists; in 27 countries (29%), an oncologist provided care for 1,000 or more patients with cancer. Twenty-five of these underserved countries were in Africa and two were in Asia; none were in Europe or the Americas.[57] Taken together, these data suggest striking disparities in access to quality cancer care, with 10- to 100-fold lower access to pathology, radiation oncology, and medical oncology services in low-income countries compared with the United States and other high-income counterparts.

Another challenge is the lack of access to novel agents, related both to slower regulatory approval of drugs and the high cost. Of 196 countries, lenalidomide had been approved in 73 countries and bortezomib in 103 countries as of 2016.[9] In many countries, drug approval does not mean equal access. Poverty and lack of health insurance coverage limits access even when drugs are approved. Although absolute prices of cancer drugs are lower in low- and middle-income countries, the cost to patients is significantly higher for low- and middle-income countries when adjusted for gross domestic product per capita.[58]

High-dose chemotherapy with SCT is a standard treatment for most transplant-eligible patients with newly diagnosed MM. Multiple randomized trials have demonstrated improved progression-free survival and OS with this approach.[59] However, the rates of SCT vary widely across the world, owing to issues with access (fewer transplant centers and mostly in larger cities), availability (limited infrastructure and trained health care personnel), and costs associated with SCT (lack of insurance coverage; Fig. 4). Most of sub-Saharan Africa has little or no access to SCT. In countries like India, the rates of SCT are approximately 20% for patients even in major academic centers in larger cities.[60]

Diagnosis and Treatment of MM in Resource-Constrained Settings

The observed differences in outcomes for patients in low- and middle-income countries are largely driven by a difference in access, fewer hospitals, fewer trained health care personnel, poor health insurance coverage, and limited or delayed access to novel therapies. A sustained effort from governments, hospitals, doctors, and professional organizations will be needed to address these disparities. There are examples of some global initiatives that have worked successfully. Organizations like ASCO and academic medical centers in high-income countries have collaborated with local hospitals to provide education and training as well as the necessary infrastructure to provide high-quality cancer care. A good example is the Uganda Cancer Institute–Fred Hutch collaboration established in 2008.[61] As a result of this alliance, a large cancer institute with clinical, laboratory, and research facilities was opened in Kampala, Uganda, in 2015. Fourteen physicians completed training in Seattle, Washington, and returned to Kampala to provide clinical and research leadership at the Uganda Cancer Institute. Collaborative clinical trials focused on improved diagnostics and treatment of breast cancer and lymphoma have been launched.[61] This alliance and other such examples provide a roadmap for future initiatives to help improve cancer care globally.

A second area of focus would be to develop standard treatment guidelines that are focused on resource-constrained settings. These guidelines should be developed by physicians in low- and middle-income countries and should address the limitations of access and establish minimum standards for the diagnosis and management of myeloma.[60] Professional bodies such as the Asian Myeloma Network and the International Myeloma Foundation have outlined guidelines for the diagnosis and management of

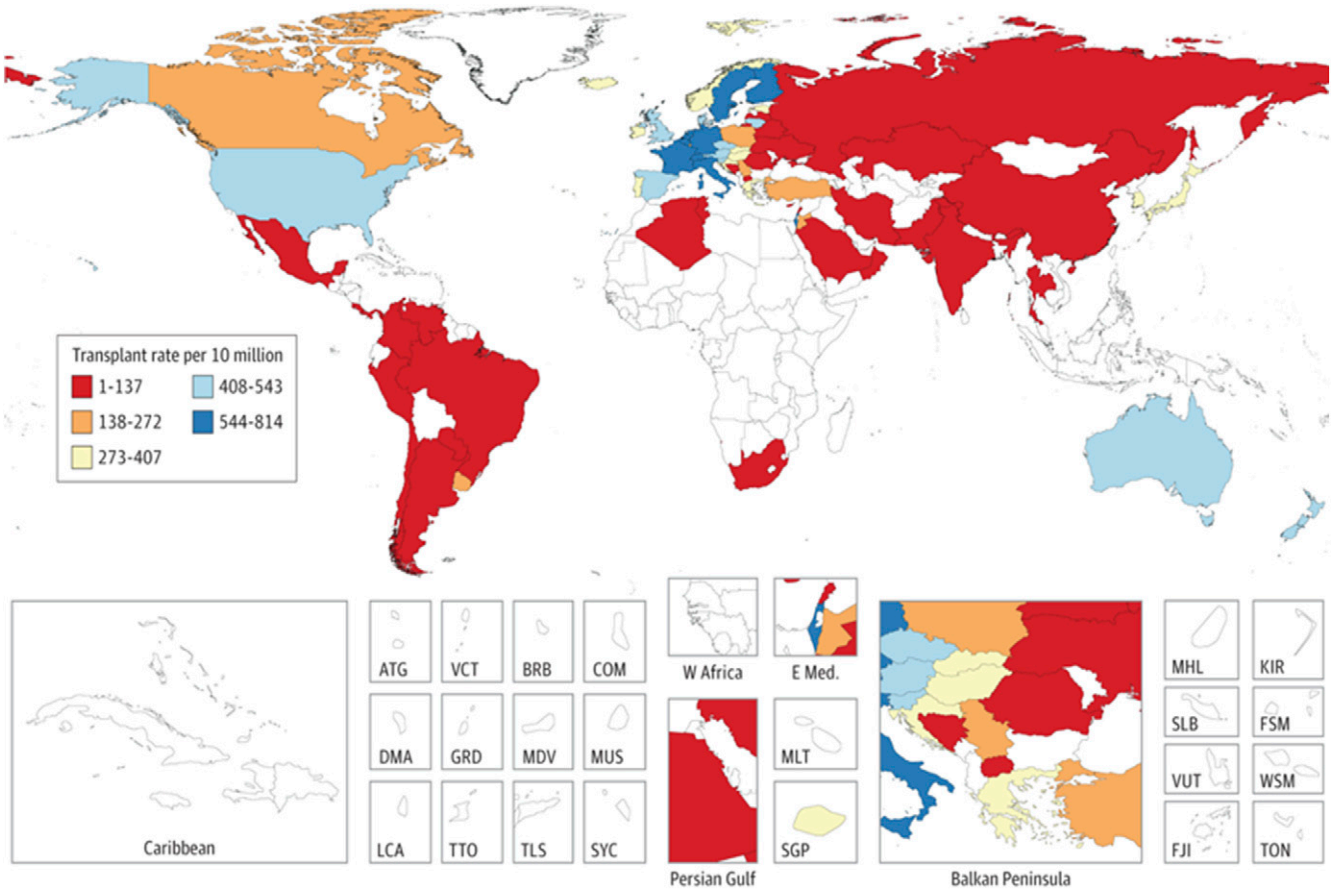

FIGURE 4. Global Stem Cell Transplantation Rate per 10 Million, 2010

Abbreviations: ATG, Antigua and Barbuda; VCT, Saint Vincent and the Grenadines; BRB, Barbados; COM, Comoros; DMA, Dominica; GRD, Grenada; MDV, Maldives; MUS, Mauritius; LCA, Saint Lucia; TTO, Trinidad and Tobago; TLS, Timor-Leste; SVC, Seychelles; MLT, Malta; SGP, Singapore; MHL, Marshall Islands; KIR, Kiribati; SLB, Solomon Islands; FSM, Federated States of Micronesia; VUT, Vanuatu; WSM, Samo (Formerly Western Samoa); FJI, Fiji; TON, Tonga.

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MM in resource-constrained settings,[53] and such guidelines must be updated as new advances and treatments become available. Novel mechanisms of health care delivery that are cost-efficient should be explored. For instance, studies from India have demonstrated the feasibility and equivalent efficacy of the use of noncryopreserved stem cells for SCT in MM.[60,62] This approach has reduced SCT costs by about 15%. Most importantly, global and governmental measures to address fundamental issues such as poverty, increased government spending on health care (including cancer care), and provision of universal basic health care are critical to high-quality, sustainable cancer care globally.[61,63]

In summary, although outcomes for patients with MM have improved in the past two decades, substantial disparities are noted globally, across rural-urban settings, and among different races and ethnicities. Available evidence suggests that, if guideline-based myeloma care is provided, outcomes across different patient strata are similar, which further suggests that access to health care may be a crucial factor for the disparities observed.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
3. Thorsteinsdottir S, Dickman PW, Landgren O, et al. Dramatically improved survival in multiple myeloma patients in the recent decade: results from a Swedish population-based study. Haematologica. 2018;103:e412-e415.
4. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122-1128.
5. Ailawadhi S, Frank RD, Sharma M, et al. Trends in multiple myeloma presentation, management, cost of care, and outcomes in the Medicare population: a comprehensive look at racial disparities. Cancer. 2018;124:1710-1721.
6. Ailawadhi S, Bhatia K, Aulakh S, et al. Equal treatment and outcomes for everyone with multiple myeloma: are we there yet? Curr Hematol Malig Rep. 2017; 12:309-316.
7. Henley SJ, Anderson RN, Thomas CC, et al. Invasive cancer incidence, 2004-2013, and deaths, 2006-2015, in nonmetropolitan and metropolitan counties - United States. MMWR Surveill Summ. 2017;66:1-13.
8. Elsayed AG, Adler W, Lebowicz Y. Multiple myeloma survival in a rural population. Biomed J Sci Tech Res. 2017;1:579-585.
9. Cowan AJ, Allen C, Barac A, et al. Global burden of multiple myeloma: a systematic analysis for the Global Burden of Disease Study 2016. JAMA Oncol. 2018; 4:1221-1227.
10. Elsayed AG, Adler W. Survival and disease characteristics of multiple myeloma in a rural population. Blood. 2014;124 (abstr 5674).
11. Lonial S, Boise LH, Kaufman J. How I treat high-risk myeloma. Blood. 2015;126:1536-1543.
12. Mateos MV, San Miguel JF. Management of multiple myeloma in the newly diagnosed patient. Hematology (Am Soc Hematol Educ Program). 2017; 2017:498-507.
13. Usmani SZ, Seifter E. Treatment approach for young, fit, newly diagnosed multiple myeloma patients. Hematology (Am Soc Hematol Educ Program). 2018; 2018:97-102.
14. Alexander DD, Mink PJ, Adami HO, et al. Multiple myeloma: a review of the epidemiologic literature. Int J Cancer. 2007; 120(Suppl 12):40-61.
15. Baker A, Braggio E, Jacobus S, et al. Uncovering the biology of multiple myeloma among African Americans: a comprehensive genomics approach. Blood. 2013; 121:3147-3152.
16. Ailawadhi S, Jacobus S, Sexton R, et al. Disease and outcome disparities in multiple myeloma: exploring the role of race/ethnicity in the Cooperative Group clinical trials. Blood Cancer J. 2018;8:67.
17. Manojlovic Z, Christofferson A, Liang WS, et al. Comprehensive molecular profiling of 718 multiple myelomas reveals significant differences in mutation frequencies between African and European descent cases. PLoS Genet. 2017;13:e1007087.
18. Ailawadhi S, Aldoss IT, Yang D, et al. Outcome disparities in multiple myeloma: a SEER-based comparative analysis of ethnic subgroups. Br J Haematol. 2012; 158:91-98.
19. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood. 2010; 116:5501-5506.
20. Morgan GJ, Davies FE, Linet M. Myeloma aetiology and epidemiology. Biomed Pharmacother. 2002;56:223-234.
21. Gebregziabher M, Bernstein L, Wang Y, et al. Risk patterns of multiple myeloma in Los Angeles County, 1972-1999 (United States). Cancer Causes Control. 2006; 17:931-938.
22. Schriber JR, Hari PN, Ahn KW, et al. Hispanics have the lowest stem cell transplant utilization rate for autologous hematopoietic cell transplantation for multiple myeloma in the United States: a CIBMTR report. Cancer. 2017;123:3141-3149.
23. Hari PN, Majhail NS, Zhang MJ, et al. Race and outcomes of autologous hematopoietic cell transplantation for multiple myeloma. Biol Blood Marrow Transplant. 2010;16:395-402.
24. Verma PS, Howard RS, Weiss BM. The impact of race on outcomes of autologous transplantation in patients with multiple myeloma. Am J Hematol. 2008; 83:355-358.
25. Joshua TV, Rizzo JD, Zhang MJ, et al. Access to hematopoietic stem cell transplantation: effect of race and sex. Cancer. 2010;116:3469-3476.
26. Fiala MA, Finney JD, Stockerl-Goldstein KE, et al. Re: disparities in utilization of autologous hematopoietic cell transplantation for treatment of multiple myeloma. Biol Blood Marrow Transplant. 2015;21:1153-1154.

27. Al-Hamadani M, Hashmi SK, Go RS. Use of autologous hematopoietic cell transplantation as initial therapy in multiple myeloma and the impact of socio-geo-demographic factors in the era of novel agents. Am J Hematol. 2014;89:825-830.
28. Costa LJ, Huang J-X, Hari PN. Disparities in utilization of autologous hematopoietic cell transplantation for treatment of multiple myeloma. Biol Blood Marrow Transplant. 2015;21:701-706.
29. Mahajan S, Tandon N, Kumar S. The evolution of stem-cell transplantation in multiple myeloma. Ther Adv Hematol. 2018;9:123-133.
30. Bhatnagar V, Wu Y, Goloubeva OG, et al. Disparities in black and white patients with multiple myeloma referred for autologous hematopoietic transplantation: a single center study. Cancer. 2015;121:1064-1070.
31. Pulte D, Redaniel MT, Brenner H, et al. Recent improvement in survival of patients with multiple myeloma: variation by ethnicity. Leuk Lymphoma. 2014; 55:1083-1089.
32. Ailawadhi S, Frank RD, Advani P, et al. Racial disparity in utilization of therapeutic modalities among multiple myeloma patients: a SEER-medicare analysis. Cancer Med. 2017;6:2876-2885.
33. Fiala MA, Wildes TM. Racial disparities in treatment use for multiple myeloma. Cancer. 2017;123:1590-1596.
34. Warren JL, Harlan LC, Stevens J, et al. Multiple myeloma treatment transformed: a population-based study of changes in initial management approaches in the United States. J Clin Oncol. 2013;31:1984-1989.
35. Wolfson JA, Sun CL, Wyatt LP, et al. Impact of care at comprehensive cancer centers on outcome: results from a population-based study. Cancer. 2015; 121:3885-3893.
36. Ailawadhi S, Advani P, Yang D, et al. Impact of access to NCI- and NCCN-designated cancer centers on outcomes for multiple myeloma patients: a SEER registry analysis. Cancer. 2016;122:618-625.
37. Go RS, Bartley AC, Crowson CS, et al. Association between treatment facility volume and mortality of patients with multiple myeloma. J Clin Oncol. 2017; 35:598-560.
38. Costa LJ, Hari PN, Kumar SK. Differences between unselected patients and participants in multiple myeloma clinical trials in US: a threat to external validity. Leuk Lymphoma. 2016;57:2827-2832.
39. Duma N, Azam T, Riaz IB, et al. Representation of minorities and elderly patients in multiple myeloma clinical trials. Oncologist. 2018;23:1076-1078.
40. Idossa D, Duma N, Chekhovskiy K, et al. Commentary: race and ethnicity in biomedical research: classifications, challenges, and future directions. Ethn Dis. 2018;28:561-564.
41. U.S. Census Bureau. Census Urban and Rural Classification and Urban Area Criteria. Washington, DC: U.S. Census Bureau; 2010.
42. U.S. Department of Agriculture Economic Research Service. Rural-Urban Continuum Codes. Washington, DC: U.S. Department of Agriculture; 2016.
43. U.S. Census Bureau. Measuring America: Our Changing Landscape. Washington, DC: U.S. Census Bureau; 2016.
44. Coleman EA, Lynch H, Enderlin C, et al. Initial report of a family registry of multiple myeloma. Cancer Nurs. 2009;32:456-464.
45. Rao K, Darrington DL, Schumacher JJ, et al. Disparity in survival outcome after hematopoietic stem cell transplantation for hematologic malignancies according to area of primary residence. Biol Blood Marrow Transplant. 2007;13:1508-1514.
46. Lipe BC, Lansigan F, Gui J, et al. Bone marrow transplant for multiple myeloma: impact of distance from the transplant center. Clin Adv Hematol Oncol. 2012; 10:28-32.
47. Wong Doo N, Coory M, White V, et al; IMPROVE Project. Low uptake of upfront autologous transplantation for myeloma in a jurisdiction with universal health care coverage: a population-based patterns of care study in Australia. Clin Lymphoma Myeloma Leuk. 2014;14:61-67.
48. Unger JM, Moseley A, Symington B, et al. Geographic distribution and survival outcomes for rural patients with cancer treated in clinical trials. JAMA Netw Open. 2018;1:e181235.
49. Piana R. "Patients With Cancer in Rural America Remain Underserved." ASCO Post, November 25, 2018. http://www.ascopost.com/issues/november-25-2018/patients-with-cancer-in-rural-america-remain-underserved/. Accessed March 14, 2019.
50. Centers for Disease Control and Prevention. New CDC report shows deaths from cancer higher in rural America. https://www.cdc.gov/media/releases/2017/p0706-rural-cancer-deaths.html. Accessed March 14, 2019.
51. Landgren O, Graubard BI, Katzmann JA, et al. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutritional Examination Survey. Leukemia. 2014;28:1537-1542.
52. Landgren O, Katzmann JA, Hsing AW, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. Mayo Clin Proc. 2007; 82:1468-1473.
53. Tan D, Chng WJ, Chou T, et al. Management of multiple myeloma in Asia: resource-stratified guidelines. Lancet Oncol. 2013;14:e571-e581.
54. Kim K, Lee JH, Kim JS, et al. Clinical profiles of multiple myeloma in Asia: an Asian Myeloma Network study. Am J Hematol. 2014;89:751-756.
55. Adesina A, Chumba D, Nelson AM, et al. Improvement of pathology in sub-Saharan Africa. Lancet Oncol. 2013;14:e152-e157.
56. International Atomic Energy Agency. Directory of Radiotherapy Centres (DIRAC). Vienna, Austria: International Atomic Energy Agency; 2015.
57. Mathew A. Global survey of clinical oncology workforce. J Glob Oncol. 2018;4:1-12.
58. Goldstein DA, Clark J, Tu Y, et al. A global comparison of the cost of patented cancer drugs in relation to global differences in wealth. Oncotarget. 2017; 8:71548-71555.

59. Dhakal B, Szabo A, Chhabra S, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. JAMA Oncol. 2018;4:343-350.

60. Kumar L, Kumar Sahoo R. Management of multiple myeloma in resource-constrained settings. Semin Oncol. 2016;43:690-694.

61. Engel M. Closing the breast cancer divide in sub-Saharan Africa. https://www.fredhutch.org/en/news/center-news/2017/08/closing-breast-cancer-divide-in-sub-saharan-africa.html. Accessed March 14, 2019.

62. Kayal S, Sharma A, Iqbal S, et al. High-dose chemotherapy and autologous stem cell transplantation in multiple myeloma: a single institution experience at All India Institute of Medical Sciences, New Delhi, using non-cryopreserved peripheral blood stem cells. Clin Lymphoma Myeloma Leuk. 2014;14:140-147.

63. Hogan DR, Stevens GA, Hosseinpoor AR, et al. Monitoring universal health coverage within the Sustainable Development Goals: development and baseline data for an index of essential health services. Lancet Glob Health. 2018;6:e152-e168.