

Consensus Statement: Importance of Timely Access to Multiple Myeloma Diagnosis and Treatment in Central America and the Caribbean

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Abstract

Background: In Central America and the Caribbean, multiple myeloma (MM) patients face significant barriers to diagnosis and treatment. The aim of this study is to describe the current situation of MM in the region, discuss the current barriers to timely diagnosis and proper treatment, and develop consensus recommendations to address these issues.

Methods: Nine experts from five countries took part in a virtual consensus meeting on MM in Central America and the Caribbean. During the meeting, experts analyzed the disease burden, the current conditions for disease management, and access to treatment in the region. The participants reached a consensus on the extent of the problem and the necessary measures.

Results: Hard evidence on the incidence and prevalence of MM in the region is scarce, but the experts perceive an increase in MM cases. The lack of data on the direct and indirect costs at the local and regional levels obscures the impact of the disease and limits awareness

among decision-makers. Most patients are diagnosed late and face long waiting times and geographical barriers to access treatment. Access to efficacious innovative therapies that increase survival time is limited due to access barriers within health systems.

Conclusions: There was consensus on five recommendations: 1) to generate evidence; 2) to educate the public; 3) to increase timely diagnosis and facilitate access to treatment; 4) to promote interaction, collaboration, and participation among all sectors involved in the decision-making process; and 5) to guarantee timely access to new therapies.

Keywords: Lymphocytes; Myelodysplastic syndromes; Multiple myeloma; Cytogenetics and molecular genetics; Stem cell transplantation

Introduction

Multiple myeloma (MM) is a cancer of bone marrow plasma cells, and globally accounts for 1% of all cancers and approximately 10% of all blood cancers. The risk of MM increases with age; most people diagnosed with MM are approximately 65 years old [1, 2].

Although MM is a chronic illness with no definitive cure, many patients continue to live full and productive lives for years or even decades following diagnosis when effective and alternative palliative treatments are available and accessible [3, 4].

Studies show a global increase in the incidence of the disease, by as much as 126% between 1990 and 2016 [5]. The regions with the highest rates of MM include Asia, North America, and Eastern Europe [6]. Medical specialists have also observed an increase in cases in Central America and the Caribbean. The causes of this increase are unknown but generally attributed to improved diagnostic methods, an increase and equitable distribution of experts in the disease, and an improved ability among general physicians and other specialists to identify its signs and symptoms, leading to a higher number of cases referred and diagnosed.

The World Health Organization (WHO) has designated September 5 as World Multiple Myeloma Day [7], to increase

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disease awareness. Several patient advocacy groups are active in Central America and the Caribbean; their efforts mainly focus on improving access to medication. That said, very few organizations in the region address the disease directly, and in some countries, no such groups exist.

Despite progress in recognizing and diagnosing the condition, many significant barriers remain, such as the limited number of specialists, a lack of timely access to their services, and inadequate training of health care professionals to identify and diagnose MM.

The scientific and medical communities are in the process of developing national consensus statements and treatment guidelines, but such initiatives are still in their early phases. While governments in the region have prioritized cancer, MM generally has a low profile among cancers. As a result, it is not considered important enough to be prioritized on national health care agendas, and governments have been slow to create policies and initiatives to address it. For all these reasons, decision-makers have little awareness of MM.

This document describes the current situation of MM in the Central America and the Caribbean regions, highlighting the main barriers and challenges, and includes consensus recommendations on strategies to reduce the burden of disease and improve the quality of life of patients.

Materials and Methods

On December 17, 2018, a meeting of hematology experts in Latin America was convened virtually. The purpose of the meeting was to review existing literature about the burden and impact of MM, discuss the current barriers to timely diagnosis and proper treatment, and develop consensus recommendations on addressing these issues. Participants included nine experts from five countries in Central America and the Caribbean with expertise in clinical practice, academia and research, and patient education and support. Third-party consultants were used to facilitate discussion.

Prior to the meeting, a draft document was prepared and circulated that summarized the existing evidence on MM in the region. During the meeting, data were presented, and group discussions followed. Topics included incidence, prevalence, and burden of disease in Latin America, the current approach to diagnosis and disease management, and access to innovative therapies. Meeting facilitators used a list of validation questions to guide discussion. For each topic, there were two rounds of questions through which experts shared opinions and provided recommendations. The process resulted in expert consensus on the topics discussed and the measures needed to address it.

Based on these results, recommendations were generated on how to raise the level of awareness of MM and ensure policy decision-makers are well informed about the disease, and what policy changes are needed to facilitate access to best possible treatment for patients with this condition.

The Institutional Review Board approval is not applicable for the study. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Incidence, prevalence, and disease burden

MM rates vary among regions, but not to a significant degree. In 2020, the Global Cancer Observatory reported the global incidence of MM to be 1.8 cases per 100,000 people. In the Caribbean, the incidence was 2.3 with a mortality rate of 1.7 per 100,000; in Central America, it was 1.6 with a mortality of 1.1 [8].

Incidence increases progressively with age, peaking among patients aged between 50 and 70. The disease is slightly more common among men than women, with African American and Afro-Caribbean men at higher risk than Caucasian, Japanese, and Hispanic counterparts. Among African Americans, MM ranks as one of the 10 cancers with the highest mortality rates [9].

Unofficial data supplied by the physicians who contributed to this consensus statement indicate an increase in MM cases in Central America and the Caribbean. The experts reported an increase of one to two new cases per month, but official statistics do not exist for these countries. In addition to increasing cases, the experts reported seeing more patients develop MM at a younger age (under 60 years old). Improved diagnostic methods, increased numbers of hematologists, and a better understanding of the disease among general practitioners and specialists, among other factors, may have contributed to a timely identification of the condition.

The burden of disease of MM in Central America and the Caribbean is difficult to quantify due to limited data collection, the absence of standardized patient records, and its exclusion from lists of notifiable diseases. While international registries exist, these often report estimates that do not accurately reflect conditions at the country level. Since Central America and the Caribbean lack high-quality demographic studies, rigorous and up-to-date data on disease rates and prevalence in the region are not available. The current information includes isolated data collected in specialized medical settings, making it impossible to accurately estimate the incidence and prevalence of MM [10].

Impact on patients' lives

MM behaves differently from person to person and can range from a slow to an aggressive progression. The signs and symptoms vary and may even be absent in the initial stages, making diagnosis difficult. Bone pain is the most frequent symptom [11], affecting 60-80% of patients at the time of diagnosis [3]. Spinal pain, loss of appetite/weight loss, fatigue, weakness in the legs, nausea, constipation, and abdominal pain may occur as well. Associated symptoms can include bone lesions (higher risk of fractures), hypercalcemia, low blood counts (especially anemia), kidney disease, and a higher risk of infections [12]. Doctors report that as many as 50% of patients present with moderate anemia. Impaired renal function can cause kidney problems in approximately 25-30% of patients. Infections are the leading cause of mortality from MM and are seven to 15

times more common in patients with this disease than in patients hospitalized for other reasons. Infections tend to be bacterial, located in the lungs and urinary tract, but can also be viral (herpes zoster in particular) or fungal [13].

A 2019 study of patients in Brazil, Panama, Mexico, Guatemala, Chile, and Colombia reported high rates of comorbidity in MM patients, including a variety of chronic diseases and other medical conditions. Approximately 53% of patients in the study had one or two comorbidities, and approximately 15% had more than two, among them are high blood pressure (29%), diabetes mellitus (12.8%), and heart disease (8%). MM patients also had a tendency of bone disease (7.2%) and kidney disease (11.1%) [14].

In addition to its physical symptoms, MM affects patients' mental and emotional health. A 2015 Spanish study found that MM patients required high levels of physical assistance, which significantly impacted their quality of life. Most patients suffer from fatigue, insomnia, and anxiety, affecting their productivity and earning power [3].

Limited support is available from patient groups in the region. Patient advocacy groups include the Guatemalan Multiple Myeloma Association, the Foundation for Patients with Multiple Myeloma in the Dominican Republic, and the Multiple Myeloma Patients Group in Panama. Most groups are relatively new organizations focused on facilitating treatment access rather than pursuing formal activities with the capacity to influence public health policies related to MM.

Costs and economic impact

The economic consequences of MM affect both patients and health systems. For patients, they include high out-of-pocket costs due to insufficient health care financing and coverage. For health systems, slow and insufficient access to treatment creates increased demand and health costs.

Given the physical and psychological problems associated with the disease and their effects on patients' functionality and productivity, MM also directly affects national productivity and economic development.

Though no information is available on the economic burden of the disease in Central America and the Caribbean, experts believe it to be high, particularly among younger patients forced to abandon their jobs and lose their ability to contribute to their households. In addition, MM patients require prolonged periods of hospitalization, generating substantial costs for patients and health systems. Early diagnosis and timely access to high-quality treatment would mean higher survival rates and improved quality of life for patients, as well as fewer complications. Conversely, delayed diagnosis and treatment have an increased burden on health systems, as more services are required as the condition progresses, such as additional emergency room (ER) visits due to fractures [15].

Diagnosis and disease management

Due to symptom variability and lack of specificity, patients' first point of contact is often a general practitioner or physician

in a different specialty who usually explores other diagnoses before testing for MM.

The 2019 study undertaken in Brazil, Panama, Mexico, Guatemala, Chile, and Colombia found that hematologists were the first point of contact for 24.9% of MM patients, followed by internists and general practitioners at 15.4%. The process for confirming diagnosis after the first patient visit can be prolonged, usually taking approximately 2 years. Most patients are diagnosed late due to a combination of factors such as nonspecific symptoms, lack of knowledge of the disease among the general population and physicians in other specialties, and the need for evaluation by a range of medical specialists [14].

Clinical suspicion or discovery of MM requires a series of studies to confirm the diagnosis, establish a prognosis, and decide on the best treatment. The process includes blood and urine tests, biopsies, and imaging studies such as X-rays and magnetic resonance imaging (MRI).

Confirming a diagnosis of MM requires specialized tests such as flow cytometry and immunohistochemistry of bone marrow tissue obtained through biopsy. All patients diagnosed with MM should also undergo karyotyping and fluorescence *in situ* hybridization (FISH) to identify chromosomal alterations that could help establish prognosis and treatment. In addition, biopsy and bone marrow aspiration help determine the volume of plasma cells and tumor load. Access to many of these tests is homogenous across Central America and the Caribbean, where basic exams for diagnosis are generally available, but specialized exams and genetic testing are not. Many such tests are not reimbursed, need to be sent abroad for processing, or are available only after long wait times at specialized facilities, leading to high costs for patients financially and in terms of prognosis [9].

Once a diagnosis is confirmed, disease management by a hematologist is essential. While no official standardized statistics exist regarding the number of specialists in each country, waiting times and geographical barriers are often obstacles to treatment and, therefore, adequate disease management.

The availability of practical clinical guides for MM varies. Health care institutions have protocols for diagnostic criteria and patient management, but few standardized national guides or consensus documents have been developed. In Latin America, Colombia and Peru have clinical guidelines, while Mexico has a consensus on diagnosing MM. In Central America and the Caribbean, such initiatives are under development.

Among the barriers to disease diagnosis and management are late diagnosis due to non-specificity of symptoms; lack of general knowledge about the disease or the role of hematologists; lack of timely access to medical specialists; and the absence of a multidisciplinary approach by a team that includes hematologists, oncologists, orthopedists, neurosurgeons, internists, nephrologists, cardiologists, psychiatrists, psychologists, and palliative care experts.

Access to adequate and effective treatment

Even in the pre-diagnosis phase of MM, monitoring is possible to gauge the condition's progression. Once the diagnosis

is confirmed, treatment occurs in different stages: induction therapy (first-line or initial treatment), followed by consolidation or maintenance therapy after achieving total or partial remission. Symptomatic patients are also evaluated and classified according to age and the presence of any comorbidities to determine suitability for a bone marrow transplant. For those who are suitable, initial therapy will probably include a combination of treatments, such as directed therapy, immunotherapy, corticosteroids, and, sometimes, chemotherapy. Following a bone marrow transplant, patients receive additional therapies to prevent a recurrence of MM, and reduce the duration of hospitalization [16, 17].

Treatment has improved notably in recent years, and combination therapy is increasingly common. First-line therapies (the first in a series of therapeutic measures taken to treat a disease) for MM can involve a combination of new and innovative medications or a combination of these medications and one or more so-called standard therapies [18]. The introduction of monoclonal antibodies as a first-line treatment has changed the treatment panorama for MM. Studies have shown that the inclusion of monoclonal antibodies contributes to better response rates and longer survival rates without disease progression [1, 18].

Although innovative therapies have shown excellent efficacy in slowing the disease's progression, offering better response rates and longer remission times, these medications are prescribed at lower rates in Central America and the Caribbean than in developed countries, due to physicians' lack of familiarity with their uses and access barriers within health systems. In many countries of the region, innovative therapies for MM are not covered by the public sector or by health insurance, requiring patients to pay for treatment out of pocket. This has led some patients to resort to legal action to obtain access to treatment. In countries where the drugs are available and covered, patients still face multiple administrative or bureaucratic obstacles that can significantly delay the delivery process, such as the timely update of national formularies.

The prognosis for patients with MM depends to a large degree on individual factors. While the disease is progressive and incurable, therapeutic advances have boosted survival rates to more than 5 years. Nevertheless, the more prolonged the treatment, attrition rates increased (from 32% to 61% and from 14% to 38% for second- and third-line treatment, respectively) due to adverse outcomes, comorbidities, or death [19]. Evidence shows that, for patients with MM, each additional line of therapy is associated with patient resistance to treatment, leading to lower response rates, shorter remission times, and higher rates of toxicity, side effects, and comorbidity [20]. Even more important, patient quality of life decreases substantially with each additional line of treatment [21, 22]. From the very beginning, administering the most effective treatment is essential for achieving lasting control over the disease and longer survival rates. Effective treatment must be offered from the start, not withheld until the second or third line of treatment [19].

Conventional medications are readily available at the regional level, among them thalidomide, bisphosphonates, cyclophosphamide, melphalan, and corticosteroids. Innovative therapies such as bortezomib, lenalidomide, pomalidomide, and daratumumab are also available. However, access to this

type of treatment is limited and complex, primarily due to government purchasing processes and delays in the inclusion of new therapies in national formularies.

The medical experts who participated in this consensus statement noted the challenges posed by new technologies. Coverage lists are not updated fast enough to include them, and there are few opportunities to collaborate on innovative access methods that facilitate the sustainable adoption of new medications. In addition, evaluations of health care technologies are based chiefly on cost-effectiveness and safety criteria that do not necessarily consider patient needs (i.e., improved quality of life and more prolonged remissions), as well as multi-criteria evaluations to assess their therapeutic value. Even when medications are available and covered, administrative obstacles and bureaucracy delay delivery times, discouraging patients from completing the process and doctors from prescribing them.

Discussion

MM is a chronic disease with multifactorial causes. The latest evidence has shown the importance of timely delivery of effective first-line treatment to offer patients better survival rates and fewer medium- and long-term complications. The disease's symptoms and complications with its progression significantly impact patients' quality of life physically, emotionally, socially, and functionally. Therefore, timely treatment is essential for reducing complications, prolonging remission times, and improving quality of life and survival rates for those who suffer from it.

While rigorous data do not exist about the actual incidence of MM in the region, the prevalence of the disease in Central America and the Caribbean is believed to have increased progressively due, in large part, to greater awareness among physicians in other specialties. General public awareness of MM remains low, however. While governments throughout the region have broadly promoted cancer on their health agendas, MM has little visibility, perhaps because of the complexity of the disease and the lack of reliable statistics about its prevalence.

Lack of awareness surrounding the disease results in delayed diagnosis because its symptoms are often nonspecific and may be associated with other conditions, complicating, and delaying the process of consulting a physician for diagnosis and treatment. Evaluations for the disease are complex, with a variety of tests required for a definitive diagnosis. Some of these tests involve specialized procedures whose cost is often, at least in part, passed on to patients.

The delays and difficulties in accessing specialists and the lack of a multidisciplinary and comprehensive approach to MM are obstacles to adequate treatment. The symptoms, characteristics, and possible complications associated with the disease often require a multidisciplinary approach, including a team of hematologists, oncologists, orthopedists, neurosurgeons, internists, nephrologists, cardiologists, psychiatrists, psychologists, and palliative care experts, among others.

Communication between health care personnel and patients, and appropriate follow-up of the disease's progression,

are fundamental to ensure treatment compliance. The lack of unified and standardized criteria in clinical treatment guides for controlling and managing MM is a significant barrier to an appropriate treatment of it. Access to adequate and effective treatment for managing the disease represents a significant barrier, given that health systems do not have at their disposal all the treatment options that offer the best results for patients.

Finally, training and educating health care professionals about the latest developments in the comprehensive management of MM, empowering and encouraging the creation of patient organizations, and addressing structural barriers to access within health systems are all critical to furthering patients' rights to access the best treatment available.

To overcome these challenges, the following recommendations are made.

Generate evidence that gives the problem greater visibility and informs decision-making

1) Strengthen mechanisms for gathering information that make it possible to compile standardized data about the disease burden and impact of MM; 2) Support medical research and participation in local and international clinical trials for evaluating the efficacy and effectiveness of current therapies. 3) Include MM on the list of reportable diseases to facilitate case registration and quantify the disease burden. 4) Include patients in generating evidence about MM and its impact on quality of life.

Educate the public about the disease, its symptoms, and its impact on patient quality of life

1) Develop wide-reaching educational campaigns to raise awareness of MM and the role of hematologists in treating it, underscoring the importance of timely diagnosis; 2) Develop and implement educational programs about MM among patients, families, and support groups to promote timely diagnosis and improve patient compliance, remembering that MM is a chronic condition.

Strengthen the capacity of the health system to offer universal access, with an emphasis on unified criteria that promotes timely diagnosis and access to treatment

1) Advocate for the timely access, coverage, and provision of health services for cancer patients; 2) Promote comprehensive disease management and the creation of multidisciplinary treatment teams; 3) Develop and implement clinical guides for general practitioners and specialists (for example, orthopedists, physiatrists, internists, nephrologists) to facilitate early detection and diagnosis; 4) Develop and implement evidence-based clinical guides for managing the disease that include the indication and use of innovative therapies, considering the need to train primary care physicians and specialists in diagnosing, treating, and monitoring the disease, thereby ensuring uniform

and standardized patient management; 5) Promote the use of telemedicine to orient primary care physicians and specialists in diagnosing and referring patients.

Promote interaction, collaboration, and participation among all sectors involved in the decision-making process

1) Train and empower patient organizations to develop skills, strategies, and actions for influencing public health policy, giving them active participation in the decision-making process, and considering their needs when proposing solutions; 2) Generate spaces for discussion among patients, physicians, service providers, and decision-makers to further solutions that consider the full range of perspectives.

Guarantee access to new therapies that address patient needs effectively

1) Promote access to new therapies with higher efficacy rates and better safety records; 2) Develop campaigns to raise decision-makers' awareness of chronic diseases that have no cure, emphasizing the value of beginning with the most effective treatments for improving patient quality of life and lengthening remission times; 3) Encourage partnership among interest groups such as patient organizations, medical and scientific groups, and the pharmaceutical industry to raise decision-makers' awareness of the importance of optimized access to therapies that meet patients' needs and ensure that such therapies are available and consistent; 4) Promote constant dialogue and collaboration with the pharmaceutical industry and establish innovative funding mechanisms to facilitate sustainable access to medication; for example, risk-sharing mechanisms in the form of pilot projects that improve the use of country resources and encourage the use of these mechanisms.

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Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

All authors read and approved the manuscript, and each author believes that the manuscript represents honest work. All authors discussed the results and contributed to the final manuscript.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article. Also, the data that supports the consensus of this article are available from the corresponding author, upon reasonable request.

Abbreviations

MM: multiple myeloma; WHO: World Health Organization

References

1. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC, Costello C, et al. Multiple myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(2):230-269.
2. American Cancer Society (n.d.) What is multiple myeloma. Available from: <https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html>.
3. Asociacion Espanola de Afectados por Linfoma, Mieloma y Leucemia (AEAL). (n.d.). El mieloma multiple, una enfermedad poco frecuente que requiere atencion integral. Available from: <http://www.aeal.es/el-mieloma-multiple-una-enfermedad-poco-frecuente-que-requiere-atencion-integral/#>.
4. Oncosalud. AUNA. Guia de Practica Clinica Manejo Multidisciplinario de Mieloma Multiple. 2018. Available from: <https://marketing.oncosalud.pe/hubfs/Guia%20especializada%20Auna/GPC%20myeloma%20multiple%20GA.DC.G.01.pdf>.
5. Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, Foreman K, et al. Global burden of multiple myeloma: a systematic analysis for the global burden of disease study 2016. *JAMA Oncol*. 2018;4(9):1221-1227.
6. Ramon-Rodriguez L, Rivera-Keeling C, Arencibia-Nunez A, Avila-Cabrera O, Izquierdo-Cano L, Espinosa-Estrada E, et al. Caracterizacion clinica y de laboratorio del mieloma multiple en el Instituto de Hematologia e Inmunologia. *Rev Cubana Hematol Inmunol Hemoter*. 2013;29(4).
7. Fernandez Aguila JD. 5 de septiembre: Dia Mundial del Mieloma Multiple. *Revista Cubana de Hematologia, Inmunologia y Hemoterapia*. 2016;32(4).
8. International Agency for Research on Cancer (IARC). GLOBOCAN 2020: Multiple Myeloma. 2020. Available from: <https://gco.iarc.fr/today/data/factsheets/cancers/35-Multiple-myeloma-fact-sheetpdf>.
9. Martinez-Cornejo TL, Najera-Martinez J, Torres-Alarcon CG, Hernandez-Bueno AI, Garcia-Castillo C, Campos-Cortes A, et al. Prevalencia de mieloma multiple en un hospital nacional de referencia de la Ciudad de Mexico de 2011 a 2016. *Hematol Mex*. 2020;21(1):32-40.
10. Pena C, Rojas C, Rojas H, Soto P, Cardemil D, Aranda S, Contreras C, et al. [Survival of 1,103 Chilean patients with multiple myeloma receiving different therapeutic protocols from 2000 to 2016]. *Rev Med Chil*. 2018;146(7):869-875.
11. De la Pena-Celaya J, Aguilar-Luevano J, Alcivar-Cedeno LM, Alvarez-Vera JL, Anaya-Cuellar I, Anorve-Hernandez E, et al. Consenso Mexicano de Mieloma Multiple. *Gaceta Medica de Mexico*. 2020;157(Supl.2).
12. Alvarado-Ibarra M, Alvarez-Vera JL, Anaya-Cuellar I, de la Pena-Celaya A, Garcia-Fernandez L, Hernandez-Ruiz E, et al. Primer Consenso Nacional de Mieloma Multiple por Hematologos del ISSSTE. *Rev Hematol Mex*. 2015;16(4):306-332.
13. Garcia-Sanz R, Victoria Mateos M, San Miguel J. Mieloma multiple. *Medicina Clinica*. 2007;129(3):104-115.
14. Tietsche de Moraes Hungria V, Chiattonne C, Pavlovsky M, Abenoza LM, Agreda GP, Armenta J, Arrais C, et al. Epidemiology of hematologic malignancies in real-world settings: findings from the Hemato-Oncology Latin America Observational Registry Study. *J Glob Oncol*. 2019;5:1-19.
15. Zhao AL, Shen KN, Wang JN, Huo LQ, Li J, Cao XX. Early or deferred treatment of smoldering multiple myeloma: a meta-analysis on randomized controlled studies. *Cancer Manag Res*. 2019;11:5599-5611.
16. Comert M, Gunes AE, Sahin F, Saydam G. Quality of life and supportive care in multiple myeloma. *Turk J Haematol*. 2013;30(3):234-246.
17. American Cancer Society. Opciones de tratamiento para el mieloma multiple segun la etapa. (n.d.). Available from: <https://www.cancer.org/es/cancer/myeloma-multiple/tratamiento/segun-la-etapa.html>.
18. Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastiris E, Goldschmidt H, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. *J Clin Oncol*. 2016;34(13):1544-1557.
19. Fonseca R, Usmani SZ, Mehra M, Slaveev M, He J, Cote S, Lam A, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. *BMC Cancer*. 2020;20(1):1087.
20. Facon T, San-Miguel J, Usmani S, Dimopoulos MA,

- Kumar S, Mateos MV, et al. A Network Meta-Analysis (NMA) to evaluate comparative effectiveness of frontline treatments for patients with Newly Diagnosed Multiple Myeloma (NDMM) who are Transplant Ineligible (TIE). *Blood*. 2019;134(Suppl_1):2144.
21. Despiegel N, Touboul C, Flinois A, Saba G, Suzan F, Gonzalez-McQuire S, Bonnetain F. Health-related quality of life of patients with multiple myeloma treated in routine clinical practice in France. *Clin Lymphoma Myeloma Leuk*. 2019;19(1):e13-e28.
22. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, Safaei R, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol*. 2016;175(2):252-264.