Patients Age 40 Years and Younger With Multiple Myeloma Have the Same Prognosis as Older Patients: An Analysis of Real-World Patients' Evidence From Latin America

Humberto Martínez-Cordero, MD, MSc[1,2]; Camila Peña, MD[3]; Natalia Paola Schutz, MD, MSc[4]; Virginia Bove, MD[5]; Fiorella Villano, MD[6]; Cecilia Beltran, MD[7]; Javiera Donoso, MD[8]; Hernán López-Vidal, MD[9]; Macarena Alejandra Roa Salinas, MD[3]; Pablo Soto, MD[10]; Paola Ochoa, MD[11]; Patricio Duarte, MD[12]; Guillermina Remaggi, MD[13]; Ariel Corzo, MD[14]; Claudia Shanley, MD[15]; Sergio Lopresti, MD[16]; Sergio Orlando, MD[17]; Verónica Verri, MD[18]; Luis Darío Quiroga, MD[19]; Dorotea Fantl, MD[4]; Jhoanna Ramirez, MD[20]; Alejandro Ospina-Idárraga, MD[1]; Henry Idrobo, MD[21]; Guillermo Quintero, MD, MBA[22]; Rigoberto Gomez, MD[23]; Omar Cantú-Martínez, MD[24]; David Gomez-Almaguer, MD[25]; Guillermo J. Ruiz-Arguelles, MACP, FRCP[26]; Kenny Mauricio Galvez-Cárdenas, MD[27]; Luis Antonio Salazar, MD[28]; Isabella Novoa-Caicedo, MD[29]; María Cynthia Fuentes-Lacouture, MD[2]; Paola Spirko, MD[1]; María Isabel Arbeláez, MD[1]; Mario Pereira, MD[1]; Jaime Valdes, MD[1]; Jule Vasquez, MD[30]; Alana von Glasenapp, MD[31]; and Eloísa Riva, MD[32]; on behalf of GELAMM (Grupo de Estudio Latinoamericano de Mieloma Múltiple)

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ABSTRACT

PURPOSE Multiple myeloma (MM) is a highly heterogeneous, incurable disease most frequently diagnosed in the elderly. Therefore, data on clinical characteristics and outcomes in the very young population are scarce.

PATIENTS AND METHODS We analyzed clinical characteristics, response to treatment, and survival in 103 patients with newly diagnosed MM age 40 years or younger compared with 256 patients age 41-50 years and 957 patients age 51 years or older.

RESULTS There were no statistical differences in sex, isotype, International Scoring System, renal involvement, hypercalcemia, anemia, dialysis, bony lesions, extramedullary disease, and lactate dehydrogenase (LDH). The most used regimen in young patients was cyclophosphamide, bortezomib, dexamethasone, followed by cyclophosphamide, thalidomide, dexamethasone and bortezomib, thalidomide, dexamethasone. Of the patients age 40 years or younger, only 53% received autologous stem-cell transplant (ASCT) and 71.1% received maintenance. There were no differences in overall survival (OS) in the three patient cohorts. In the multivariate analysis, only high LDH, high cytogenetic risk, and ASCT were statistically associated with survival.

CONCLUSION In conclusion, younger patients with MM in Latin America have similar clinical characteristics, responses, and OS compared with the elderly.

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INTRODUCTION

Multiple myeloma (MM) is a heterogeneous disease most often diagnosed in people older than 65 years, and it is very rare in people younger than 40 years. Data on clinical characteristics, response to treatment, and survival in this younger population are scarce. Unfortunately, even in this young group, it remains incurable despite the availability of modern treatments.[1,2] The first retrospective series from the Mayo Clinic showed that patients younger than 40 years represent <3% of all patients with MM, and MM is extremely infrequent under 30 years. The MM in the young population is more frequent in men; it has a higher frequency of light chain MM, especially in those younger than 30 years, who also show significant bone involvement with extramedullary dissemination, a low monoclonal protein component, and few plasma cells in the bone marrow.[3,4] Better survival has been described in this population group of patients with MM, attributed to better tolerance to chemotherapy and because within the studied cohorts, there is a percentage of patients with lower tumor burden and the absence of renal involvement whose survival could exceed 8 years, even before new therapies were introduced.[3,4] The average number of years of life lost in patients with MM is more significant than in many other cancers and could exceed 30 years in patients younger than 40 years of age.[5] Therefore, the younger population with MM would require a different therapeutic approach in the era of new therapies. This article presents the demographic and clinical characteristics of response to treatment and survival of our population younger than

CONTEXT

Key Objective

The key objective of this manuscript is to highlight the behavior of young patients with multiple myeloma (MM) in Latin America, in order to define if there is any difference in the clinical behavior of these patients and if they deserve a different approach.

Knowledge Generated

The knowledge generated by this manuscript emphasizes that these patients could have a similar behavior to the rest of the population; however, it also highlights the difficulty in accessing consolidation therapies such as hematopoietic stem cell transplantation in Latin America, thus, generating a urgent need to correct the needs in access to these therapies. It also highlights their impact on the evolution of the disease over time.

Relevance

To our knowledge, this is one of the few studies that focus on young patients with MM in order to evaluate their clinical behavior. With these results we can impact the necessary consolidation therapies for young patients with the disease, in whom the requirement for innovative treatments is accentuated.

40 years, specifically in Latin American patients belonging to the Grupo de Estudio Latinoamericano de Mieloma Múltiple (GELAMM) database.

PATIENTS AND METHODS

We analyzed newly diagnosed multiple myeloma (NDMM) patients younger than 40 years who received treatment for MM using international myeloma working group (IMWG) criteria for diagnosis in six Latin American countries between 2010 and 2018 from the GELAMM database. Demographics and disease features were analyzed using descriptive statistics. We included the variables of age, sex, isotype, International Scoring System, renal involvement (creatinine ≥2), hypercalcemia (calcium ≥10), anemia (hemoglobin ≤10), dialysis, bony lesions, extramedullary disease, high lactate dehydrogenase (LDH), high-risk cytogenetics (CG; t4;14, t14;16, del 17p), treatment received, response to treatment (pre- and post-transplant), maintenance therapy, and overall survival (OS). Differences in clinical presentation between groups were compared using the chi-square test and standardized mean differences (SMDs). Estimates of OS within age groups were produced using the Kaplan-Meier method and were compared using the log-rank test among the age population. Multivariate analysis was performed using Cox regression analysis. Progression-free survival (PFS) was not analyzed because of the missing data.

Patients with smoldering (asymptomatic) myeloma, amyloidosis, and monoclonal immunoglobulin M–related disorders were not included. All analyses were performed using the statistical package SPSS version 25 (Armonk, NY).

RESULTS

One thousand three hundred sixteen patients were included in this analysis. Of the total database, 7.8% were patients younger than 40 years. The median age of all combined cohorts was 53.81 years, whereas the median age of younger patients was 35.14 years, and 64.1% were male. The presenting features of patients age 40 years and younger compared with other age populations are shown in Table 1.

Regarding treatment, cyclophosphamide, bortezomib, dexamethasone (CyBorD) was the most used regimen, followed by cyclophosphamide, thalidomide, dexamethasone (CTD) and bortezomib, thalidomide, dexamethasone (VTD) in the younger population; lenalidomide was only prescribed as a frontline regimen in four patients, 3.9%, which was similar in the older population (Table 2). Fifty-five patients (53%) in this younger population received high-dose therapy and autologous stem-cell transplantation (ASCT), and only 45% received maintenance therapy without bone marrow transplant.

The type of maintenance received was thalidomide in 47.7%, lenalidomide in 45.3%, bortezomib in 4.5%, and others in 2.3%.

The overall response rate in ASCT was 78.8% (Table 3). For patients younger than 40 years, it was 78.6%; in patients age 41-50 years, it was 78.6%; and it was 80.3% in patients older than 50 years.

The overall response rate post-ASCT was 93% in patients younger than 40 years, 94.2% in patients age 41-50 years, and 94.4% in those older than 50 years, indicating that ASCT deepens responses achieved at the induction time. An interesting finding is that patients age 40 years or younger tend to achieve more complete responses after bone marrow transplant than patients in the group of 41 to 50 years and older than 51 years (34.9% *v* 24.6%, *v* 28.7%, respectively; Table 4).

With a median follow-up of 32 months (range, 1-113), the median OS for the entire cohort was 85 months (95% CI, 81.413 to 88.587), with no statistically significant

TABLE 1. Clinical Characteristics of the Patients at Diagnosis Stratified by Age Group

Characteristic	Overall	≤40 Years	41-50 Years	>50 Years[a]	*P*	SMD
No.	1,316	103	256	957		
Age, years, mean (SD)	53.81 (8.14)	35.14 (4.38)	46.05 (2.96)	57.90 (4.05)	<.001	3.888
Sex, male, No. (%)	706 (53.6)	66 (64.1)	140 (54.7)	500 (52.2)	.068	0.161
Isotype, No. (%)					.193	0.184
IgG	730 (56.9)	53 (53.5)	134 (53.8)	543 (58.0)		
IgA	221 (17.2)	14 (14.1)	51 (20.5)	156 (16.7)		
Light chain	240 (18.7)	21 (21.2)	41 (16.5)	178 (19.0)		
Other	93 (7.2)	11 (11.1)	23 (9.2)	59 (6.3)		
ISS, No. (%)					.585	0.119
1	296 (26.5)	27 (29.7)	64 (29.1)	205 (25.4)		
2	344 (30.8)	30 (33.0)	61 (27.7)	253 (31.4)		
3	478 (42.8)	34 (37.4)	95 (43.2)	349 (43.2)		
Renal disease, No. (%)	291 (24.3)	26 (28.6)	58 (25.1)	207 (23.7)	.554	0.075
Anemia, No. (%)	677 (51.4)	44 (47.8)	132 (55.9)	501 (56.7)	.261	0.074
Hypercalcemia, No. (%)	199 (17.0)	14 (15.4)	38 (17.4)	147 (17.1)	.906	0.035
Dialysis, No. (%)	89 (8.1)	7 (8.8)	23 (10.6)	59 (7.3)	.266	0.078
Bony lesions, No. (%)	781 (77.4)	60 (78.9)	136 (73.1)	585 (78.3)	.3	0.091
Extramedullary disease, No. (%)	298 (22.6)	23 (22.3)	59 (23.0)	216 (22.6)	.984	0.011
High LDH, No. (%)	213 (29.9)	14 (20.9)	47 (33.6)	152 (30.1)	.174	0.192
High-risk cytogenetics, No. (%)	59 (13.4)	4 (15.4)	13 (14.0)	42 (13.1)	.931	0.044

NOTE. SMDs < 0.2 indicate no relevant remaining imbalance between populations.
Abbreviations: Ig, immunoglobulin; ISS, International Scoring System; LATAM, Latin America; LDH, lactate dehydrogenase; MM, multiple myeloma; SD, standard deviation; SMD, standardized mean differences.
[a]Age cutoff points were calculated considering the average age of diagnosis of MM in LATAM.

differences for the three groups ($P = .248$). The median OS for the entire cohort that did not proceed with ASCT was 53 months (95% CI, 46.8 to 59.1), whereas for the cohort that did proceed with ASCT, the median survival was not achieved ($P < .0001$; Fig 1B). No statistically significant differences across the three groups of patients taken to ASCT were observed ($P = .940$; Fig 1C). In the group 40 years or younger, the median OS in the nontransplanted group was 63 months (95% CI, 57.67 to 68.33) and 78 months (95% CI, 53.444 to 102.56) in the patients taken to ASCT ($P < .001$).

In the multivariate analysis (Table 5), the factors that independently correlated with better survival were not high LDH, not high risk, and having proceeded with ASCT.

DISCUSSION

This retrospective international multicenter cohort study focuses on the outcomes of patients age 40 years or younger with MM in our region. MM remains an incurable disease in most patients although its prognosis has improved in the past two decades.[1,6] Several factors explain this improvement

TABLE 2. Induction Regimen Received Stratified by Age Group

Regimen	Overall, No. (%)	≤40 Years, No. (%)	41-50 Years, No. (%)	>50 Years, No. (%)
CyBorD	511 (38.8)	30 (29.1)	106 (41.4)	375 (39.2)
CTD	249 (18.9)	22 (21.4)	35 (13.7)	192 (20.1)
VTD	221 (16.8)	21 (20.4)	54 (21.1)	146 (15.3)
RVD	31 (2.4)	4 (3.9)	7 (2.7)	20 (2.1)
TD	121 (9.2)	12 (11.7)	26 (10.2)	83 (8.7)
VAD	36 (2.7)	3 (2.9)	7 (2.7)	26 (2.7)
MPT	51 (3.9)	0 (0.0)	4 (1.6)	47 (4.9)
Other	96 (7.3)	11 (10.7)	17 (6.6)	68 (7.1)

Abbreviations: CTD, cyclophosphamide, thalidomide, dexamethasone; CyBorD, cyclophosphamide, bortezomib, dexamethasone; MPT, melphalan, prednisolone, thalidomide; RVD, bortezomib, lenalidomide, dexamethasone; TD, thalidomide and dexamethasone; VAD, bortezomib, doxorubicine, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

TABLE 3. Response to Induction Treatment (N = 1,316)

Response	Overall (%)	≤40 Years (%)	41-50 Years (%)	>50 Years (%)
Stringent CR	6.1	4.8	7.6	5.8
CR	15.2	22.6	11.2	15.6
VGPR	21.7	22.6	20.1	22.1
PR	35.8	28.6	39.7	36.8
SD	11.6	10.7	11.2	11.8
PD	8.4	8.3	10.3	7.9

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

TABLE 5. Multivariate Analysis

Factor	HR	95% CI	*P*
ISS stage III	0.846	0.404 to 1.771	.658
Absence of EM disease	0.971	0.418 to 2.258	.946
High LDH	2.919	1.087 to 7.840	**.034**
No high CG risk	0.422	0.186 to 0.955	**.038**
Age (<40 years *v* >40 years)[a]	0.444	0.059 to 3.319	.429
No ASCT	3.765	1.634 to 8.676	**.002**

NOTE. Bold indicates statistically significant values.
Abbreviations: ASCT, autologous stem-cell transplant; CG, cytogenetics; EM, extramedullary disease; HR, hazard ratio; ISS, International Scoring System; LDH, lactate dehydrogenase.
[a]Not significant, but included for comparison.

in survival, including the use of triple combinations, post-transplant maintenance therapy in eligible patients or continuous therapy in ineligible patients, the possibility of achieving minimal negative residual disease status, and the use of novel therapies including immuno-effector cell therapy.[7-9] The median age of patients at diagnosis of MM is 65 years. The population younger than 50 years is 13%, the population younger than 40 years is only 2.2%, and the population younger than 30 years is up to 0.3%.[3,4] Our study shows that 7.8% are 30 years old or younger, indicating that Latin America's MM population tends to be younger. However, red flags for back pain, renal failure, or anemia are more easily detectable in the young population, and we add this to the fact that MM diagnosis in the older population is sometimes difficult, even more in Latin America where access to medical specialists can be limited, these numbers must be taken cautiously.

Although several studies have shown that the clinical presentation of younger patients may differ from that of older patients, we found that the clinical characteristics that define the disease are the same in both age groups.[2-4] The treatment of MM in our study was quite heterogeneous; however, the main treatments are VTD and CyBorD, which reflects Latin American clinical practice, and access to lenalidomide, the standard of care in other latitudes, was only offered to very few patients.[10,11]

TABLE 4. Response After Transplant (n = 679) With 55 Patients Age 40 Years or Younger

Response	Overall	≤40 Years	41-50 Years	>50 Years
ASCT, No. (%)	679 (100)	53.4	58.6	49.5
Responses (%)				
Stringent CR	17.8	20.9	16.4	17.8
CR	28.7	34.9	24.6	28.7
VGPR	26.8	18.6	31.1	26.8
PR	21.1	18.6	22.1	21.1
SD	4.7	4.7	4.9	4.7
PD	0.9	2.3	0.8	0.9

Abbreviations: ASCT, autologous stem cell transplant; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Similarly, consolidation with high doses of chemotherapy and autologous cell salvage was offered only to 53% of patients, and maintenance to less than half, which denotes the marked disparities with other latitudes.[12,13] The response to induction treatment was similar in the three cohorts, and the post-transplant response in patients who achieved transplantation tended to be slightly better in patients younger than 40 years. The OS of our entire cohort is 85 months, which is lower than that reported for populations treated with similar schemes.[14] The prognosis of patients younger than 40 years has been reported to be better than that in the older population when they present with favorable risk factors, which did not occur in our study.[3,4] This could also be explained by the high number of patients who were not taken for transplantation, thus reflecting an unmet need for treatment in Latin America. Despite the prognosis seeming to be better in other studies, the years of life lost clearly in this population are many, reaching up to more than 30 years.[5] The preceding shows that the therapeutic approach of these patients must be different, considering the possible better tolerance to more intensive treatments where, without a doubt, the new therapeutic options will play a fundamental role.[15,16]

Among the limitations of our study are the low number of patients, the inability to measure PFS to the main treatments used, and the nonregistration of data on toxicity.

In conclusion, in this Latin American multicenter study, we found that the young population with MM has similar presentation characteristics to elderly patients. A significant amount of information is lost regarding the risk characterization, especially regarding CG. Regarding treatment, less than half of the patients achieve a very good partial response or better. It is striking that more than a third of these young patients did not have access to high doses of chemotherapy and bone marrow transplantation.

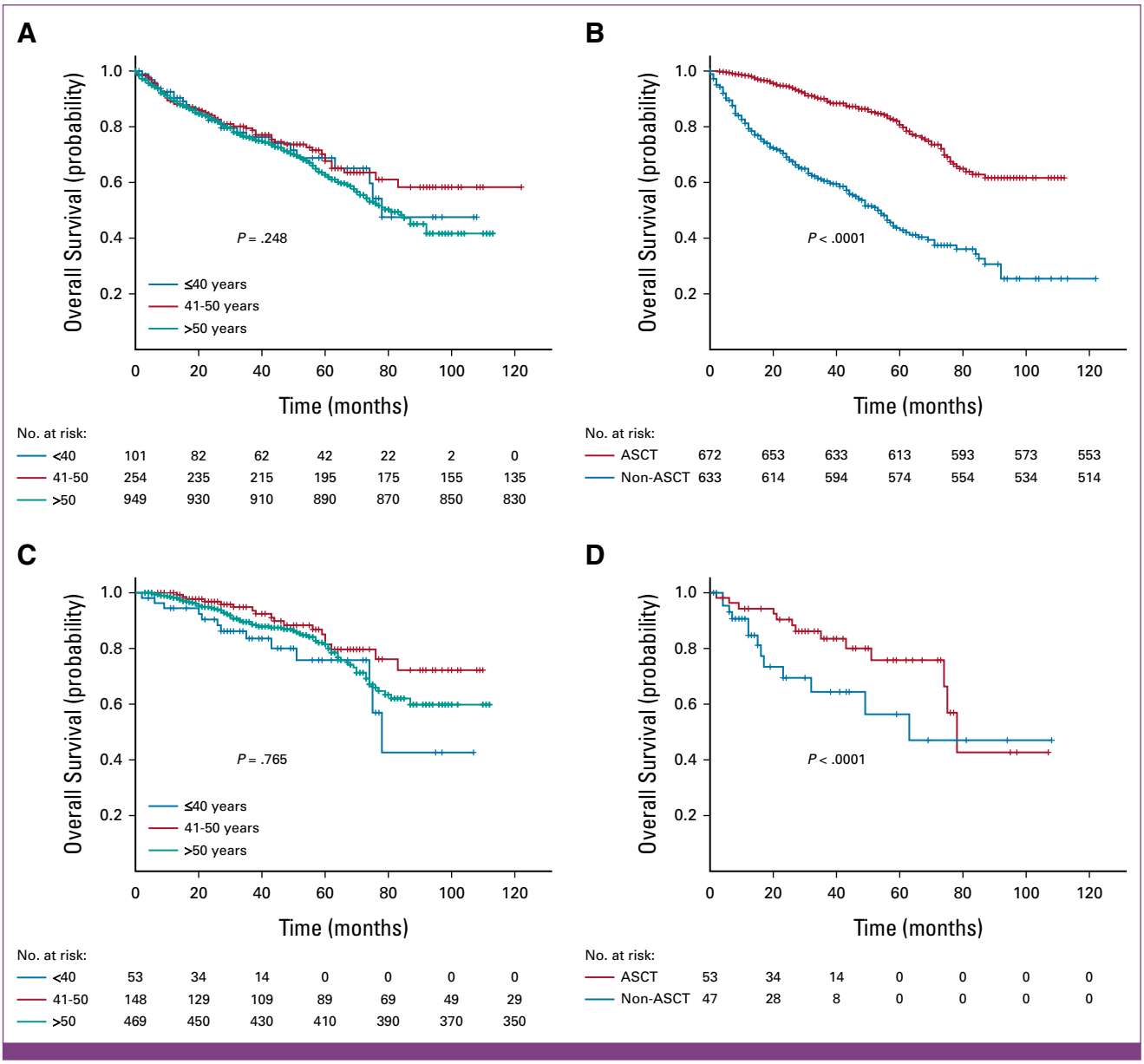

FIG 1. Survival analyses. (A) Overall survival for the entire cohort. (B) Transplanted (red line) *v* nontransplanted (blue line) patients in the entire cohort. (C) The entire cohort of patients undergoing ASCT. (D) Only patients age 40 years or younger ASCT (red line) versus non-ASCT (blue line). ASCT, autologous stem-cell transplant.

Maintenance therapy is offered to less than half of the patients. The median OS is lower than that in other series of patients younger than 40 years, even than in the elderly cohorts. Prospective multicentric studies are required to elucidate the behavior of the disease in this group of patients.

AFFILIATIONS

[1]Instituto Nacional de Cancerología de Colombia, Bogotá, Colombia
[2]Hospital Militar Central, Bogotá, Colombia
[3]Departamento de Hematología, Hospital Del Salvador, Santiago, Chile
[4]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
[5]Asociación Española, Montevideo, Uruguay
[6]CASMU, Montevideo, Uruguay
[7]Hospital de Temuco, Temuco, Chile
[8]Hospital Sótero del Río, Santiago, Chile
[9]Hospital Barros Luco, Santiago, Chile
[10]Hospital Dr. Eduardo Schütz Schroeder, Puerto Montt, Chile
[11]Instituto Alexander Fleming, Munro, Argentina
[12]CEMIC University Hospital, Buenos Aires, Argentina
[13]Fundaleu, Buenos Aires, Argentina
[14]Hospital de Clínicas, Buenos Aires, Argentina
[15]Hospital Británico, Buenos Aires, Argentina
[16]Hospital Posadas, El Palomar, Argentina
[17]Hospital Rossi, La Plata, Argentina
[18]IDIM, Buenos Aires, Argentina

[19]Hospital Churruca, Buenos Aires, Argentina
[20]Hospital IESS, Guayaquil, Ecuador
[21]Hospital Universitario Del Valle Evaristo García E.S.E, Cali, Colombia
[22]Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia
[23]Instituto Catalán de Oncología, Cali, Colombia
[24]Hospital Universitario, Universidad Autónoma de Nuevo León, Monterrey, México
[25]Hospital Universitario Dr. José Eleuterio González, Monterrey, México
[26]Centro De Hematología Y Medicina Interna, Puebla, México
[27]Hospital Pablo Tobón Uribe, Medellín, Colombia
[28]Clínica FOSCAL, Bucaramanga, Colombia
[29]Facultad de Medicina, Universidad El Bosque. Bogotá, Colombia
[30]Instituto Nacional De Enfermedades Neoplásicas, Lima, Perú
[31]ReVita, Centro Oncológico Integral, Asunción, Paraguay
[32]Hospital de Clínicas, Montevideo, Uruguay

CORRESPONDING AUTHOR

Humberto Martínez-Cordero, MD, MSc, Instituto Nacional de Cancerología, Hospital Militar Central, Bogotá, Colombia; e-mail: humbertomartinez48@gmail.com.

AUTHOR CONTRIBUTIONS

Conception and design: Humberto Martínez-Cordero, Camila Peña, Natalia Paola Schutz, Patricio Duarte, Ariel Corzo, Sergio Orlando, Dorotea Fantl, Alejandro Ospina-Idárraga, Henry Idrobo, Guillermo Quintero, Omar Cantú-Martínez, David Gomez-Almaguer, Kenny Mauricio Galvez-Cárdenas, Luis Antonio Salazar, María Isabel Arbeláez, Jaime Valdes, Eloísa Riva
Administrative support: Humberto Martínez-Cordero, Rigoberto Gomez, Luis Antonio Salazar, Isabella Novoa-Caicedo
Provision of study materials or patients: Cecilia Beltran, Javiera Donoso, Patricio Duarte, Ariel Corzo, Verónica Verri, Luis Darío Quiroga, Dorotea Fantl, Jhoanna Ramirez, Alejandro Ospina-Idárraga, Rigoberto Gomez, Guillermo J. Ruiz-Arguelles, Luis Antonio Salazar, Isabella Novoa-Caicedo, Paola Spirko, Jaime Valdes, Jule Vasquez
Collection and assembly of data: Humberto Martínez-Cordero, Camila Peña, Natalia Paola Schutz, Virginia Bove, Fiorella Villano, Cecilia Beltran, Javiera Donoso, Hernán López-Vidal, Macarena Alejandra Roa Salinas, Paola Ochoa, Patricio Duarte, Guillermina Remaggi, Ariel Corzo, Claudia Shanley, Sergio Lopresti, Sergio Orlando, Verónica Verri, Luis Darío Quiroga, Dorotea Fantl, Jhoanna Ramirez, Alejandro Ospina-Idárraga, Henry Idrobo, Guillermo Quintero, Rigoberto Gomez, Omar Cantú-Martínez, Kenny Mauricio Galvez-Cárdenas, Luis Antonio Salazar, María Cynthia Fuentes-Lacouture, Paola Spirko, Jaime Valdes, Jule Vasquez, Alana von Glasenapp, Eloísa Riva
Data analysis and interpretation: Humberto Martínez-Cordero, Camila Peña, Ariel Corzo, Sergio Orlando, Dorotea Fantl, Jhoanna Ramirez, Alejandro Ospina-Idárraga, Henry Idrobo, Guillermo Quintero, Rigoberto Gomez, David Gomez-Almaguer, Guillermo J. Ruiz-Arguelles, Kenny Mauricio Galvez-Cárdenas, Luis Antonio Salazar, Isabella Novoa-Caicedo, Paola Spirko, Jaime Valdes, Alana von Glasenapp, Eloísa Riva
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Humberto Martinez-Cordero
Honoraria: Janssen, Sanofi, Bristol Myers Squibb/Celgene, Takeda
Consulting or Advisory Role: Janssen, Sanofi, Bristol Myers Squibb/Celgene, Takeda
Travel, Accommodations, Expenses: Sanofi

Camila Peña
Honoraria: Janssen
Consulting or Advisory Role: Janssen
Travel, Accommodations, Expenses: Varifarma

Cecilia Beltran
Consulting or Advisory Role: Takeda
Travel, Accommodations, Expenses: Janssen, Takeda

Javiera Donoso
Honoraria: Janssen Oncology
Consulting or Advisory Role: Janssen Oncology

Hernán López-Vidal
Consulting or Advisory Role: Janssen Oncology, Pfizer, AbbVie
Speakers' Bureau: Janssen Oncology
Travel, Accommodations, Expenses: Janssen Oncology, Pfizer

Macarena Alejandra Roa Salinas
Honoraria: AbbVie, AstraZeneca, Tecnofarma
Consulting or Advisory Role: Janssen, Takeda, Tecnofarma
Travel, Accommodations, Expenses: Roche

Pablo Soto
Travel, Accommodations, Expenses: Janssen

Paola Ochoa
Honoraria: Janssen, Sanofi
Consulting or Advisory Role: Sanofi, Janssen
Travel, Accommodations, Expenses: Janssen

Patricio Duarte
Consulting or Advisory Role: Janssen, Sanofi, Takeda
Speakers' Bureau: Sanofi
Travel, Accommodations, Expenses: Sanofi

Guillermina Remaggi
Consulting or Advisory Role: Janssen-Cilag, Sanofi, Pfizer
Speakers' Bureau: Janssen
Travel, Accommodations, Expenses: Janssen, Sanofi

Claudia Shanley
Honoraria: Takeda
Consulting or Advisory Role: Sanofi, AbbVie, Janssen
Travel, Accommodations, Expenses: Janssen

Sergio Lopresti
Honoraria: Janssen Oncology

Dorotea Fantl
Speakers' Bureau: Janssen, Takeda, Sanofi, Amgen
Research Funding: Janssen, Takeda, Helsinn Therapeutics, Sanofi, Roche
Travel, Accommodations, Expenses: Janssen, Sanofi

Guillermo Quintero
Consulting or Advisory Role: Janssen Oncology, Pfizer, Takeda, Sanofi
Travel, Accommodations, Expenses: AbbVie, Amgen, Janssen Oncology, Roche

David Gomez-Almaguer
Consulting or Advisory Role: Janssen, Takeda, Teva, BMS

Speakers' Bureau: Bristol Myers Squibb (Mexico), AbbVie, Novartis, Janssen, Amgen, Takeda

Luis Antonio Salazar
Honoraria: Janssen, AbbVie, AstraZeneca
Consulting or Advisory Role: AstraZeneca, Janssen
Travel, Accommodations, Expenses: Janssen

María Cynthia Fuentes-Lacouture
Honoraria: Fresenius Kabi BioSimiliars
Travel, Accommodations, Expenses: Janssen

Mario Pereira
Honoraria: Novartis, Amgen, Janssen, Pint Pharma
Consulting or Advisory Role: Novartis
Travel, Accommodations, Expenses: AbbVie

Jule Vasquez
Honoraria: Janssen, Roche
Consulting or Advisory Role: Janssen, AbbVie
Research Funding: Roche (Inst)
Travel, Accommodations, Expenses: Janssen, AbbVie

Eloísa Riva
Honoraria: Sanofi, Janssen, AbbVie/Genentech
Research Funding: Sebia (Inst)
Travel, Accommodations, Expenses: Roemmers, Janssen, Sanofi

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