Original article
Rev Hematol Mex. 2019 October-December;20(4):262-272.

Revista de Hematología

Epidemiological characteristics at time of diagnosis of three hematological neoplasms of lymphoid origin in a domestic reference hospital.

Características epidemiológicas al momento del diagnóstico de tres neoplasias hematológicas de origen linfoide en un hospital de referencia nacional

María de Jesús Nambo-Lucio,[1] Neri Natividad Muñoz,[1] Sergio Adrián Cleto-Gutiérrez,[1] José Alberto Regalado-Ramos,[2] Miguel Ángel Herrera-Rojas[2]

Abstract

OBJECTIVE: To identify the demographic, clinical characteristics and the most frequently prescribed treatments of patients with diagnosis of non-Hodgkin mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) or multiple myeloma (MM) who received care at a Mexican hospital.

MATERIAL AND METHOD: A retrospective study was conducted, analyzing the clinical records of patients with diagnosis of MCL, CLL, or MM who received care at the Siglo XXI National Medical Center Cancer Hospital Hematology Service from June 2008 to October 2016.

RESULTS: 399 patients were included, 214 (54%) men, with median age of 60 years (38 to 88). The distribution was 31 (8%) patients with MCL, 21 (5%) with CLL, and 347 (87%) with MM. The most common initial clinical manifestation was weight loss in MCL and CLL, and lumbar pain in MM. The median time for a patient to see a doctor was greater in patients with MM than in MCL and CLL (7.2 *vs* 5 and 6 months). The common denominator in the three neoplasms was that most of patients were in an advanced stage of the disease at the time of diagnosis.

CONCLUSION: Most of demographic characteristics of patients included were similar to those described in the literature; however, the age of patients with myeloma was lower, the time to diagnosis was greater and stage of disease at diagnosis was higher than expected.

KEYWORDS: Non-Hodgkin mantle cell lymphoma; chronic lymphocytic leukemia; Multiple myeloma.

Resumen

OBJETIVO: Identificar las características demográficas, clínicas y los tratamientos más prescritos de los pacientes con diagnóstico de linfoma no Hodgkin de células del manto, leucemia linfocítica crónica o mieloma múltiple.

MATERIAL Y MÉTODO: Estudio retrospectivo que analizó las características clínicas de pacientes con diagnóstico de linfoma no Hodgkin de células del manto, leucemia linfocítica crónica o mieloma múltiple que recibieron atención en el Servicio de Hematología del Hospital Centro Médico Nacional Siglo XXI de junio de 2008 a octubre de 2016.

RESULTADOS: Se incluyeron 399 pacientes, 214 (54%) hombres, con mediana de edad de 60 años (38 a 88). La distribución fue: 31 (8%) pacientes con linfoma no Hodgkin de células del manto, 21 (5%) con leucemia linfocítica crónica y 347 (87%) con mieloma múltiple. La manifestación clínica inicial más común fue pérdida de peso en linfoma no Hodgkin de células del manto y leucemia linfocítica crónica, y el dolor lumbar en mieloma múltiple. El tiempo promedio para que un paciente acudiera con el médico fue mayor en pacientes con mieloma múltiple que en linfoma no Hodgkin de células del manto y leucemia linfocítica crónica (7.2 *vs* 5 y 6 meses). La mayoría

[1] Siglo XXI National Medical Center Cancer Hospital, Hematology and Bone Marrow Transplant Service, IMSS, Mexico City.
[2] Janssen-Cilag SA de CV.

Received: 4 April 2019
Accepted: 2 June 2019

Correspondence
María de Jesús Nambo Lucio
marynambo@yahoo.com.mx

This article must be quoted
Nambo-Lucio MJ, Muñoz NN, Cleto-Gutiérrez SA, Regalado-Ramos JA, Herrera-Rojas MA. Epidemiological characteristics at time of diagnosis of three hematological neoplasms of lymphoid origin in a domestic reference hospital. Hematol Méx. 2019 October-December;20(4):262-272.
https://doi.org/10.24245/rhematol.v20i4.3515

de los pacientes estaban en una etapa avanzada de la enfermedad al momento del diagnóstico de las tres neoplasias.

CONCLUSIÓN: La mayor parte de las características demográficas de los pacientes fueron similares a las descritas en la bibliografía; sin embargo, la edad de los pacientes con mieloma fue menor, el tiempo para el diagnóstico fue mayor y la etapa de la enfermedad al momento del diagnóstico fue mayor de lo esperado.

PALABRAS CLAVE: Linfoma no Hodgkin de células del manto; leucemia linfocítica crónica; mieloma múltiple.

INTRODUCTION

Hematologic neoplasms are a cause of high morbimortality worldwide. Mexico has developed a Histopathologic Registry of Malignant Neoplasms[1,2] for reporting of new cases; however, it is crucially important to know the demographic characteristics and most widely used diagnostic methods in our population. Based on global cancer statistics (Globocan 2018), leukemia, non-Hodgkin lymphoma (NHL), and multiple myeloma are among the 25 most common neoplasms.[3] NHL is in 13th place worldwide and its incidence has risen, probably related to advances in diagnostic techniques and the appearance of acquired immunodeficiency syndrome in the late 20th Century.[4] NHL constitutes a heterogeneous group of neoplasms of lymphoid origin with significant histological and clinical differences, usually with nodal presentation and immunophenotype B in 70% to 90% of cases.[5] According to the World Health Organization, one of the variants of NHL is mantle cell lymphoma (MCL), which originates in B cells and is characterized by small monomorphic cells with irregular nuclei, cyclin D1 overexpression, and translocation t(11;14). MCL represents 10% of NHL, has higher incidence in men around 60 years of age,[4-6] and manifests primarily by adenopathy or extranodal involvement such as infiltration to bone marrow with pancytopenia and occasionally leukocytosis. On the other hand, chronic lymphocytic leukemia (CLL) also originates in B lymphocytes, has a median age of presentation of 64 to 70 years, and is uncommon in persons under 30 years of age.[7] In the year 2016, 19,000 new cases of CLL were diagnosed in the USA,[8] with lower incidence in Asia and Latin America, including Mexico.[9] In its initial stages, it may present without clinical manifestations in 80% of patients, and when they appear they are nonspecific, like mild fever, weakness, and diaphoresis. In more advanced stages, adenopathies and splenomegaly are reported, and in some cases alterations in laboratory studies like anemia, thrombocytopenia, and elevation of lactic dehydrogenase, among others; however, an indispensable requisite for diagnosis is the presence of lymphocytosis over 5 x 10^9/L.[7] Multiple myeloma (MM) is a malignant neoplasm originating in B lymphocytes which represents 1% of all malignant neoplasms and is characterized by aberrant expression of plasma cells in bone marrow and monoclonal secretion of globulins, causing organ damage. The global incidence of MM is 1.5/100,000 inhabitants, but in some Latin American countries the incidence is as high as 14.5/100,000 inhabitants.[10] MM more commonly affects men with a median age of 70 years, and its primary clinical manifestations are bone disease (pain, lytic lesions), renal failure, anemia, signs of hypercalcemia,

and heightened risk of infection.[11] Although the etiology of leukemias, lymphomas, and myeloma is unknown, different epidemiological studies have identified risk factors which may contribute to the development of such neoplasms, such as exposure to chemical products (benzene, polycyclic hydrocarbons, pesticides, etc.), exposure to ionizing radiation, viruses, genetic factors, and immunological factors, among others.[1]

The importance of having a hospital epidemiological analysis of these 3 hematologic neoplasms lies in the possibility of ascertaining their incidence to improve the quality of diagnosis and the treatment patients receive. The objective of this study was to identify the demographic and clinical characteristics of patients with diagnosis of MCL, CLL, or MM who received care in a Mexican domestic reference hospital. Additionally, the treatments most frequently prescribed in the three diseases were analyzed.

MATERIAL AND METHOD

A retrospective study was conducted, analyzing the clinical records of patients with diagnosis of MCL, CLL, or MM who received care at the Siglo XXI National Medical Center Cancer Hospital Hematology Service, operated by the Mexican Social Security Institute (Spanish acronym IMSS) in the period to June 2008 through October 2016. The criteria for inclusion were age over 18 years; diagnosis of MCL, CLL, or MM on or after June 1, 2008; and at least one year of observation. Records with different or doubtful diagnosis and those which lacked the information necessary to cover the variables analyzed in the study were excluded. The variables included were demographic data (age, gender), clinical characteristics (symptoms, time of evolution, first manifestation, etc.), diagnostic studies used (hematic biometry, biopsy, protein electrophoresis, cytogenetics) and treatment schema used. The data were analyzed using Software Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for patients' demographic data and clinical characteristics.

RESULTS

Three hundred nine-nine cases which complied with the criteria for inclusion were included, corresponding to 214 (54%) male patients and 185 (46%) female patients with an overall median age of 60 years (range 38 to 88 years). The disease distribution was 31 (8%) patients with MCL, 21 (5%) patients with CLL, and 347 (87%) patients with MM. The clinical characteristics are shown in **Table 1**.

Characteristics of patients with mantle cell lymphoma

The 31 patients included in the MCL group included 23 (74%) male and 8 (26%) female patients, with median age of 64 years (range 40 to 84 years). At the time of diagnosis, 21 patients presented with one or more comorbidities, such as a history of heart disease (n = 11, 35%), type 2 diabetes (n = 9, 29%), high blood pressure (n = 3, 10%), and renal failure (n = 2, 6%); no patient had human immunodeficiency virus (HIV) infection. The median time of evolution from onset of symptoms until a diagnosis was established was 5 months with a range of 1 to 12 months, and the initial symptoms were weight loss (n = 21, 68%), diaphoresis (n = 15, 48%), and fever (n = 7, 22%), whereas physical exploration documented splenomegaly and hepatomegaly in 13 (42%) and 7 (22%) patients, respectively. Adenopathies were found in 30 (97%) patients with a median diameter of 5 cm (range 2 to 20 cm) and in 7 (22%) patients a Bulky mass more than 10 cm in diameter was found. In relation to the assessment of patient function using the ECOG (Eastern Cooperative Oncology Group) scale, 13 patients had values over 2. Lactic dehydrogenase in blood

https://doi.org/10.24245/rhematol.v20i4.3515

Table 1. Comparative table of demographic and clinical characteristics of patients included

	Mantle cell lymphoma (n)	Chronic lymphocytic leukemia (n)	Multiple myeloma (n)
	31	21	347
Male/female	23/8	18/3	173/174
Median age in years	64 (40 to 80)	66 (49 to 84)	59 (38 to 88)
Comorbidities (n)	21 (68%)	12 (57%)	233 (67%)
Heart disease	11 (35%)	7 (33%)	141 (40%)
Type 2 diabetes	9 (29%)	5 (23%)	4 (1%)
High blood pressure	3 (10%)	1 (5%)	90 (26 %)
Renal failure	2 (6%)	1 (5%)	24 (7%)
HIV infection	0	0	0
Others	0	0	20 (6%)
Time in months from symptoms to contact	5 (1 to 12)	6 (1 to 24)	7.2 (< 1 to 48)
Initial symptoms (n)			
Fever	7 (22%)	7 (33%)	0
Diaphoresis	15 (48%)	11 (52%)	0
Weight loss	21 (68%)	12 (57%)	0
Lumbar pain	0	0	117 (42%)
Bone pain	0	0	43 (15%)
Others	0	0	187
ECOG > 2 (n)	13 (42%)	3 (14%)	76 (22%)
Patients with adenopathies (%)	97	100	0
Median size of adenopathies in cm (range)	5 (2-20)	2 (1-11)	-

was found to be high in 24 (75%) patients with a median of 308 U/L and range of 168 U/L to 688 U/L. Values from hematic biometry at diagnosis are shown in **Table 2**. For staging of the disease, the Ann Arbor scale was used, finding 14 (45%) patients in stage II, 7 (22%) patients in stage III, and 10 patients in stage IV (32%), with none in stage I. Ten (32%) patients presented MCL infiltration to one or more organs, including bone marrow (n = 6, 19%), Waldeyer's ring (n = 5, 16%), stomach (n = 3, 8%), liver (n = 3, 8%), intestine (n = 2, 6%), kidney (n = 1, 3%), skin (n = 1, 3%), and central nervous system (n = 1, 3%). Hospitalization was required in 26 (84%) patients, either to complement diagnosis or to begin treatment. **Table 3** shows the initial treatment regimens used.

Characteristics of patients with chronic lymphocytic leukemia

Twenty-one patients with diagnosis of CLL were included, 18 (86%) male and 3 (14%) female, with median age of 66 years (range 49 to 84 years). At the time of diagnosis, 12 patients presented with one or more comorbidities such as history of heart disease (n = 7, 33%), type 2 diabetes (n = 5, 23%), high blood pressure (n = 1, 5%), and renal failure (n = 1, 5%); no patient had human immunodeficiency virus (HIV) infection. The median time of evolution from onset of symptoms until the patient visited a hematologist was 6 months (1 to 24 months), while the time from first contact with a hematologist until a diagnosis of CLL was established

Table 2. Result of hematic biometry at diagnosis

	Mantle cell lymphoma	Chronic lymphocytic leukemia	Multiple myeloma
Patients evaluated, **n**	27	21	255
Hemoglobin, n (g/dL)			
< 8	2 (7%)	3 (14%)	35 (14%)
8-12	9 (33%)	11 (52%)	129 (50%)
> 12	16 (59%)	7 (34%)	91 (36%)
Leukocytes, n (/mm^3)			
< 1000	0	0	NA
1000-10,000	20 (74%)	0	NA
10,000-30,000	7 (26%)	15 (71%)	NA
30,000-50,000	0	5 (24%)	NA
50,000-100,000	0	1 (5%)	NA
Platelets, n (/mm^3)			
< 50,000	2 (8%)	0	3 (1 %)
50,000-100,000	6 (22%)	9 (43%)	20 (8%)
>100,000	19 (70%)	12 (57%)	232 (91%)

NA: not available.

was 30 days (range 1 to 90 days). The initial symptoms in patients with CLL were weight loss (n = 12, 57%), diaphoresis (n = 11, 52%), and fever (n = 7, 33%), whereas physical exploration documented splenomegaly and hepatomegaly in 12 (57%) and 5 (23%) patients respectively. Adenopathies were found in all patients, with a median diameter of 2 cm (range 1 to 11 cm). The most common localization of adenopathies was in axillae (n = 12, 57%) and inguinal region (n = 12, 57%), and less commonly in the neck (n = 9, 43%), supraclavicular fossa (n = 7, 33%), abdomen (n = 7, 33%), head (n = 3, 14%), and chest (n = 1, 5%). In relation to the assessment of patient function using the ECOG (Eastern Cooperative Oncology Group) scale, 3 (14%) patients had values over 2. Laboratory studies performed at the time of diagnosis (**Table 2**) found anemia in 14 (67%) patients, of whom 3 (14%) had hemoglobin below 8 g/dL and 11 (52%) had hemoglobin between 8 g/dL and 12 g/dL. Thrombocytopenia was documented with platelet counts below 100.0 x 10^3/µL in 9 (43%) patients, and the rest of the patients had platelet counts above 100.0 x 10^3/µL. In relation to total leukocyte count, 15 (71%) patients had between 10.0 x 10^3/µL and 30.0 x 10^3/µL, 5 (24%) patients had between 30.0 x 10^3/µL and 50.0 x 10^3/µL, and only one patient (5%) had between 50.0 x 10^3/µL and 100.0 x 10^3/µL leukocytes. As part of the CLL diagnosis, the total lymphocyte count in peripheral blood was taken, finding that 5 (24%) patients had 5.0 x 10^3/µL lymphocytes, 7 (33%) patients had between 5.0 x 10^3/µL and 10.0 x 10^3/µL, 4 (19%) patients had between 10.0 x 10^3/µL and 30.0 x 10^3/µL, and 5 (24%) had more than 30.0 x 10^3/µL lymphocytes. Bone marrow aspirate was taken in 15 patients, and in all cases the bone marrow was found to be infiltrated by mature lymphocytes and with absence of blasts, the median lymphocyte count in bone marrow was 60% (range 30% to 90%). Hematic cytometry was requested in only 50% of patients, with positive results for CD20 and

https://doi.org/10.24245/rhematol.v20i4.3515

Table 3. Regimens prescribed as first-line treatment

Mantle cell lymphoma, n = 31	
Regimen	**N (%)**
CDRF (cyclophosphamide, fludarabine, dexamethasone, rituximab)	15 (48)
Methotrexate	5 (16)
CEOP (cyclophosphamide, epirubicin, vincristine, and prednisone)	5 (16)
R-CHOP	4 (13)
Cyclophosphamide	1 (3)
Radiotherapy	1 (3)
Adjuvant radiotherapy	15 (48)
Chronic lymphocytic leukemia, n = 21	
Regimen	**N (%)**
FCDR (fludarabine, cyclophosphamide, dexamethasone, and rituximab)	9 (42)
CNOP (cyclophosphamide, methotrexate, vincristine, and prednisone)	5 (24)
Dexamethasone with fludarabine or cyclophosphamide	3 (14)
Methotrexate	2 (10)
Chlorambucil combined with prednisone	2 (10)
Multiple myeloma, n = 347	
Regimen	**N (%)**
DT (dexamethasone and thalidomide)	158 (45)
Dexamethasone alone	89 (26)
CMP-T (cyclophosphamide, melphalan, prednisone, and thalidomide)	32 (9)
CMOP (cyclophosphamide, melphalan, vincristine, and prednisone)	20 (6)
DAI (interferon, dexamethasone, tretinoin)	17 (5)
Melphalan with prednisone	11 (3)
Other regimens	20 (6)
Adjuvant radiotherapy	262 (75)
Biphosphonates	169 (49)
Autologous hematopoietic cell transplantation	31 (9)

CD5 in all cases; no other antigens were tested for. The ZAP-70 was performed in one patient, resulting positive. For staging of the disease, the Binet and Rai scales were used. On the Binet scale, 4 (19%) patients were found in stage A, 10 (48%) patients in stage B, and 7 (33%) patients in stage C. In the Rai classification, 2 (9%) patients were found in stage or 5 (24%) patients in stage 1, 5(24%) patients in stage 2, 4 (19%) patients in stage 3, and 5 (24%) patients in stage 4. **Table 3** summarizes the initial treatment regimens used.

Characteristics of patients with multiple myeloma

Three hundred fourty-seven patients were included in the MM group, 173 (49.5%) male and 174 (50.5%) female patients, with median age of 59 years (range 38 to 88 years). At the time of diagnosis, 114 (33%) patients had no comorbidities, while 233 patients presented with one or more comorbidities such as history of heart disease (n = 141, 40%), type 2 diabetes (n = 4, 1%), high blood pressure (n = 90, 26%), renal failure (n = 24, 7%), hypothyroidism (n =11, 3.1%), history of stroke (n = 3, 0.9%), prostate cancer (n = 3, 0.9%) or rheumatological disease (n = 3, 0.9%); no patient had human immunodeficiency virus (HIV) infection. The median time of evolution from onset of symptoms until the patient visited a hematologist was 7.2 months (range < 1 to 48 months), while the time from first contact with a hematologist until a diagnosis of MM was established was 20 days (range 6 days to 36 months). The initial symptoms in patients with MM for which they sought medical attention were lumbar pain (n = 117, 42%), bone pain dolor (n = 43, 15%), pathological fracture (n = 31, 11%), anemic syndrome (n = 18, 6%), clinical signs of renal failure (n = 8, 3%), other factors like peripheral vein thrombosis or presence of tumors (n = 59, 21%), whereas in 71 (20%) patients the primary symptom was not specified. In relation to the assessment of patient function using the ECOG (Eastern Cooperative Oncology Group) scale, 76 (22%) patients had values over 2. Laboratory studies performed at the time of diagnosis found anemia in 164 (51%) patients,

of whom 35 (14%) had hemoglobin below 8 g/dL and 129 (50%) had hemoglobin between 8 g/dL and 12 g/dL. Hemoglobin values above 12 g/dL were found in 91 (36%) patients, whereas in 92 cases the hemoglobin value at diagnosis was not documented. Thrombocytopenia was found with platelet counts below 100.0 x 10^3/µL in 23 (9%) patients, 232 patients had platelet counts above 100.0 x 10^3/µL, and in 92 cases the platelet count was not documented (**Table 2**). In relation to renal function, creatinine below 1.2 mg/dL was found in 139 (55%) patients, between 1.2 mg/dL and 2 mg/dL in 61 (24%) patients, between 2.1 mg/dL and 5 mg/dL in 33 (13%) patients, and above 5 mg/dL in 18 (7%) patients, whereas in 96 (27%) patients results were not documented. Creatinine clearance was below 60 mL/minute in 34 (10%) patients. Serum albumin levels were below 3.5 g/dL in 98 (56%) patients and above 3.5 g/dL in 78 (44%) patients and data was not obtained for 171 (49%) patients. Serum calcium was below 8.5 mg/dL in 41 (21%) patients, between 8.5 mg/dL and 10.5 mg/dL in 106 (54%) patients, between 10.5 mg/dL and 12.0 mg/dL in 31 (16%) patients, and above 12.0 mg/dL in 18 (9%) patients, while values could not be obtained in 151 cases. B2 microglobulin values could be obtained in 136 cases, of whom 49 (36%) patients had levels below 3.5 mg/L, 35 (25%) patients were between 3.5 mg/L and 5.5 mg/L, and 52 (38%) patients were over 5 mg/L. The presence of extramedullary plasmacytoma was documented in 73 (21%) patients, while infiltration of bone marrow by plasma cells was found in 274 (79%). The median plasma cell count in bone marrow was 38% (range 2% to 95%), whereas plasma cells in peripheral blood were found in 2 patients. Serum protein electrophoresis was performed in 304 (88%) patients, detecting a monoclonal IgG spike in 169 (55%) patients, IgA in 77 (25%) patients, IgE in 3(0.9%) patients, IgM in 1 (0.3%) patient, light chains in 37 (12%) patients, and non-secretory myeloma in 17 (6%) cases. In 266 image studies performed, no osteolytic lesions were detected in 11 (4%) patients, one osteolytic lesion in 19 (7%) patients, 2 lesions in 18 (7%) patients, 3 lesions in 18 (7%) patients, and more than 4 osteolytic lesions in 197 (74%) patients. **Table 3** shows the initial treatment regimens used.

DISCUSSION

Non-Hodgkin mantle cell lymphoma, chronic lymphocytic leukemia, and multiple myeloma have as a common characteristic that they are neoplasms which originate in lymphoid B cells, they present primarily in adult patients, and there is no therapeutic option which achieves a definitive cure.[12] Although hematological neoplasms are not the primary causes of death in the general population, based on global statistics, they are among the 20 most common neoplasms, making it crucially important to ascertain their incidence in Mexico, but it is also important to determine their clinical presentation and the diagnostic methods used to establish available therapeutic alternatives and choose that which offers the greatest advantages to the patient, taking into consideration quality of life, availability of treatment in Mexico, compliance with treatment, overall response, and survival. This study conducted a descriptive analysis of the number of cases of MCL, CLL, and MM diagnosed at a domestic reference medical center to gain an overview of clinical manifestations and the diagnostic methods used with such patients who are beneficiaries of a social security system. Although there are some similarities, due to the difference in diagnostic procedures and therapeutic regimes, between these 3 neoplasms, each one was analyzed separately.

MCL is an aggressive B cell lymphoma characterized by overexpression of cyclin D1 and t(11;14) translocation, with poor prognosis when compared with other histological varieties of NHL, since there is no standard treatment which

https://doi.org/10.24245/rhematol.v20i4.3515

guarantees a cure.[12] It most commonly affects men with median age at onset of 65 years. In this present study, most patients with MCL were male (74% *vs* 26%) with median age of 64 years, similar to the findings reported in the international literature.[13] The etiology of MCL is unknown; however, an increase in its incidence has been observed in recent years;[14] unfortunately, in Mexico there are no well-structured domestic statistical studies. The clinical course of the disease may be indolent or chronic in some patients,[15] for which reason many patients may take weeks or months before seeking medical care. In this study, although most patients presented symptoms like weight loss (68%), diaphoresis (48%), and even fever (22%), the time to seek medical care and establish a diagnosis was prolonged, with a median of 5 months. In relation to the stage of the disease at the time of diagnosis, in this study a majority of patients (45%) were in Ann Arbor stage II, unlike findings from other studies including patients of Hispanic origin where the majority are diagnosed in Ann Arbor stage I and only 8% are in stage II, whereas extranodal involvement was also more common than that reported in other studies (32% *vs* 14.7%).[13]

Chronic lymphocytic leukemia (CLL) is a chronic and usually indolent lymphoproliferative neoplasm, characterized by accumulation of CD5+ B cells which have a low rate of proliferation.[16] In some Latin American countries, it appears to be less common than in other regions like Europe and Asia. In Mexico, we lack detailed information but its incidence appears to be low;[17] there are only some articles on the subject, one of which is a consensus from the year 2008 which reports a low incidence of cases,[7] although it is probable that many cases have not been reported or even have not been diagnosed due to the clinical characteristics of the disease. In European countries the median age of onset is 72 years and it is twice as common in men as in women,[16,18] whereas in Mexico the median age is 63.5 years.[7] In this article we observed a median age of 66 years, similar to the findings reported previously, with higher incidence in men (86% *vs* 14%). The clinical presentation of CLL is variable, but the large majority of patients (70% to 80%) are asymptomatic at the time of diagnosis, which is often discovered incidentally when patients undergo hematic cytometry for other reasons.

When a patient with CLL presents symptoms, the most common are weakness, mild fever, weight loss, diaphoresis, and a higher rate of infection.[8] In this study, the most common initial symptoms were weight loss (57%), diaphoresis (52%), and fever (33%), while the median evolution time from onset of symptoms until the patient visited a hematologist was 6 months, a long time probably related to the ambiguity of the symptoms. In more advanced stages of the disease, adenopathies, hepatosplenomegaly, cytopenia due to medullary failure, or autoimmune processes like autoimmune hemolytic anemia or autoimmune thrombocytopenia may be evident.[19] In the patients included in this study, splenomegaly and hepatomegaly were documented in 57% and 23% respectively, while all presented adenopathies of 1 to 11 cm in diameter, most commonly located in axillae (57%) and inguinal region (57%). Thrombocytopenia with platelets $< 100.0 \times 10^3/\mu L$ was documented in 43% of patients, probably due to medullary failure and in all cases a negative Coombs test was confirmed. According to the International Working Group on CLL in 2008,[19,20] the diagnostic criteria for CLL are having a monoclonal lymphocyte count of 5000/μL or higher in peripheral blood with at least 3 months' duration and less than 55% of prolymphocytes, in addition to having a cytometry showing co-expression of CD5, CD19, CD20, and CD23. Hematic biometries which patients underwent at the time of diagnosis found that a majority (57%) had lymphocytosis between $5.0 \times 10^3/\mu L$ and $10.0 \times 10^3/\mu L$. Flow

cytometry was requested in only 50% of patients, and was positive in all cases for CD20 and CD5, with which the diagnosis of CLL was established. With an established diagnosis, the stage of the disease could be evaluated using the RAI and Binet scales to identify patients who would require observation only and those who would require treatment, finding that the majority (48%) were in the intermediate risk group. Only 38% of patients initially remained under observation; however, with the passing of time all patients required some form of treatment.

Multiple myeloma (MM) is a malignant neoplasm traditionally considered incurable, characterized by an increase in monoclonal plasma cells in bone marrow) MM represents 1% of all cancers worldwide, and its incidence is highest in men around 60 years of age and in persons with family history of MM.[10] In the group of patients included in this study, no difference was found in presentation by gender, affecting men and women equally, whereas the median age was 59 years, lower than that reported in the literature. A previous multicenter study with 2733 patients included that analyzed some racial differences in relation to myeloma, showed that the median age of Hispanic patients with myeloma was 74 years (range: 70 to 80 years).[21] At the time a diagnosis of MM was established, most patients (77%) had some concomitant disease, most commonly ischemic heart disease; other comorbidities were diabetes mellitus, high blood pressure, renal failure, etc., which may have helped reduce the intensity of the chemotherapy regimens used. The median evolution time from onset of symptoms until the patient visited a doctor was 7.2 months (range < 1 to 48 months), while the time from first contact with a hematologist until a diagnosis of MM was established was 20 days (range 6 days to 36 months). Varga et al[22] found that in a group of 193 patients with MM, the median time from onset of symptoms to diagnosis was 4.1 months (0 to 35.4 months) and to start treatment was 5.2 months, observing that the delay in starting treatment was greater in patients with better prognosis (initial stages or low-risk cytogenetics). The most common initial symptom in patients included in the study was lumbar pain in 42% of cases, followed by bone pain (15%), presence of pathological fractures (11%), anemic syndrome (6%), and clinical signs of renal failure (3%). Other reasons for which patients visited a doctor were an event of peripheral vein thrombosis or the presence of tumoral growth in 21% of cases. Such symptoms are similar to those published in the literature.[23] The functional quality of patients was found to be significantly diminished in 22% of cases, with scores above 2 on the ECOG scale and remaining bedridden more than 50% of the time and requiring care by family members or nursing. The incidence of anemia was lower than that found in other studies (64% *vs* 72%),[23] also finding thrombocytopenia in 7% of patients. Renal damage could be observed in up to 50% of patients with MM, most commonly caused by renal deposits of immunoglobulins or free chains. In this study, half of patients presented some level of renal damage with elevated levels of creatinine; however, a substantial reduction of glomerular filtrate was shown in only 10% of cases. Hypercalcemia in MM is caused primarily by an increase in bone reabsorption by osteoclasts, activated by different cytosines secreted locally by tumoral plasma cells, releasing calcium.

This phenomenon is more common in patients with a high tumor load.[24] In this study, a significant percentage of patients (25%) presented hypercalcemia, although it was above 12.0 mg/dL only in 9%. The type of immunoglobulin most commonly secreted in patients with MM is IgG, followed by IgA, and only light chains were found in only 15% of cases.[25] In this study, the most common finding was a monoclonal IgG spike (55%) followed by IgA (25%), IgE (0.9%), and IgM (0.3%), while light chains were found

https://doi.org/10.24245/rhematol.v20i4.3515

in 37 (12%) patients and 17 (6%) cases of non-secretory myeloma were diagnosed. A diagnosis of myeloma was established based on finding at least 10% of clonal plasma cells in bone marrow or having the result of a tissue biopsy compatible with plasmacytoma accompanied by hypercalcemia, anemia, renal damage, or bone disease.[26]

CONCLUSIONS

Most of demographic characteristics of patients included were similar to those described in the literature; however, the age of patients with myeloma was lower, the time to diagnosis was greater and stage of disease at diagnosis was higher than expected. This study marks a precedent and opens the door to new research studies to assess the standardization of medical care in patients with hematologic neoplasms.

REFERENCES

1. Tirado-Gómez LL, Mohar A. Epidemiología de las neoplasias hemato-oncológicas. Inst Nac Cancerol 2007;2:109-20.
2. Secretaría de Salud, Dirección General de Epidemiología. Registro histopatológico de neoplasias malignas. Compendio: mortalidad y morbilidad. 2000.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Incidence and survival in sarcoma in the United States: A focus on musculoskeletal lesions. Anticancer Res 2013;33(6):2597-604.
4. Rizo P, Sierra MI, Vázquez G, Cano M, Meneses A, Mohar A. Registro Hospitalario de Cáncer: Compendio de Cáncer 2000-2004. Inst Nac Cancerol 2007;2(2):203-87.
5. Labardini JR, Cervera E, Corrales C, Balbuena M, Barbosa A, Espinoza J, et al. Oncoguía. Linfoma no Hodgkin. Inst Nac Cancerol 2011;6:139-52.
6. Globocan 2008 [Internet]. Available from: http://www-dep.iarc.fr
7. Cano R, Alvarado M, Álvarez E, Baltazar S, Castellanos E, Castillo MH, et al. Primer consenso en leucemia linfocítica crónica de la Agrupación Mexicana para el Estudio de la Hematología: epidemiología, diagnóstico y tratamiento. Med Univ 2008;10(40):159-67.
8. Kipps TJ, Stevenson FK, Wu CJ, Croce CM, Wierda WG, Gribben J, et al. Chronic lymphocytic leukaemia. Nat Rev Dis Prim 2017;3(CII):16096. doi: 10.1038/nrdp.2016.96.
9. Hernandez-Caballero A, Arellano-Llamas AA, Cruz-Rico J, Ojeda JV, Tuna-Aguilar E, Aguayo-Gonzalez A, et al. Genetic susceptibility variants for chronic lymphocytic leukaemia in Mexican mestizos. Br J Haematol 2015;169(6):909-11. doi: 10.1111/bjh.13259.
10. Curado MP, Oliveira M, Silva D, Souza D. Epidemiology of multiple myeloma in 17 Latin American countries: an update. Cancer Med 2018;7(5):2101-8. doi: 10.1002/cam4.1347.
11. Hari P. Recent advances in understanding multiple myeloma. Hematol Oncol Stem Cell Ther 2017;10(4):267-71. doi: 10.1016/j.hemonc.2017.05.005.
12. Gordon LI, Bernstein SH, Jares P, Kahl BS, Witzig TE, Dreyling M. Recent advances in mantle cell lymphoma: Report of the 2013 Mantle Cell Lymphoma Consortium Workshop. Leuk Lymphoma 2014;55(10):2262-70. doi: 10.3109/10428194.2013.876634.
13. Wang Y, Ma S. Racial differences in mantle cell lymphoma in the United States. BMC Cancer 2014;14:1-8. doi: 10.1186/1471-2407-14-764.
14. Smedby KE, Hjalgrim H. Epidemiology and etiology of mantle cell lymphoma and other non-Hodgkin lymphoma subtypes. Semin Cancer Biol. 2011;21(5):293-8. doi: 10.1016/j.semcancer.2011.09.010.
15. Kahl BS, Dreyling M, Gordon LI, Quintanilla-Martinez L, Sotomayor EM. Recent advances and future directions in mantle cell lymphoma research: report of the 2016 mantle cell lymphoma consortium workshop. Leuk Lymphoma 2017;58(7):1561-9. doi: 10.1080/10428194.2017.1283036.
16. Crowther-Swanepoel D, Houlston RS. Genetic variation and risk of chronic lymphocytic leukaemia. Semin Cancer Biol 2010;20(6):363-9. doi: 10.1016/j.semcancer.2010.08.006.
17. Ruiz-Argüelles GJ. Advances in the diagnosis and treatment of acute and chronic leukemia in Mexico. Salud Publica Mex 2016;58(2):291-5. http://dx.doi.org/10.21149/spm.v58i2.7799
18. Horner M, Ries L, Krapcho M, Neyman N, Aminou R, Howlader, N Altekruse S, et al. SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD. 2009.
19. Rai KR, Jain P. Chronic lymphocytic leukemia (CLL)-Then and now. Am J Hematol 2016;91(3):330-40. doi: 10.1002/ajh.24282.
20. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008 Jun 15;111(12):5446-56. doi: 10.1182/blood-2007-06-093906.
21. Ailawadhi S , Frank R, Advani P, Swaika A,Temkit M, Menghani R, Sharma M, et al. Racial disparity in utilization of therapeutic modalities among multiple myeloma patients: a SEER-medicare analysis. Cancer Medicine 2017;6(12):2876-2885. doi: 10.1002/cam4.1246.

22. Varga G, Mikala G, Andrikovics H, Masszi T. How long does a myeloma patient currently wait for the diagnosis in Hungary? Orv Hetil 2014;155(39):1538-1543. doi: 10.1556/OH.2014.30000.

23. Jacob LA, Suresh Babu MC, Lakshmaiah KC, Babu KG, Lokanatha D, Rajeev LK, et al. Multiple myeloma: Experience of an institute in limited resource setting. Indian J Cancer 2017;54(1):340-2. DOI: 10.4103/ijc.IJC_87_17

24. Oyajobi BO. Multiple myeloma/hypercalcemia. Arthritis Res Ther 2007;9(Suppl.1):1-6. doi: 10.1186/ar2168

25. Rafae A, Malik MN, Zar MA, Durer S, Durer C. An overview of light chain multiple myeloma: Clinical characteristics and rarities, management strategies, and disease monitoring methods. Cureus 2018;10(8):1-13. doi: 10.7759/cureus.3148

26. Goldschmidt N, Zamir L, Poperno A, Kahan NR, Paltiel O. Presenting signs of multiple myeloma and the effect of diagnostic delay on the prognosis. J Am Board Fam Med [Internet] 2016;29(6):702-9. DOI: 10.3122/jabfm.2016.06.150393.

https://doi.org/10.24245/rhematol.v20i4.3515