Multidisciplinary diagnosis and treatment of mantle cell lymphoma

Expert consensus • Asociación Colombiana de Hematología y Oncología (ACHO)

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Abstract

Introduction: among the sub-types of lymphoma, mantle cell lymphoma, or what was previously known as intermediate lymphocytic lymphoma, accounts for 3-10% of B-cell non-Hodgkin lymphomas. Treatment is directed according to the patient's classification, age, functional status and comorbidities, and is directly related to the ability to receive intensive treatment or transplantation. It is important to homogenize treatments to offer the best alternatives in the Colombian context, as there are different diagnostic and therapeutic options today, most of which are financed by the Colombian healthcare system.

Objective: to structure a series of considerations for the diagnosis and treatment of MCL within the Colombian context.

Methods: a formal, mixed (Delphi/nominal) expert consensus was developed. The options for each question were scored in two masked rounds and an open nominal session. The information was consolidated in Excel and analyzed using STATA 13.

Results: 25 considerations were developed for the diagnosis and treatment of MCL. Twenty-two specialists participated: 16 hematologists and hematologist-oncologists, four hematopathologists, one radiation therapist and one nuclear medicine specialist from Bogotá, Medellín and Cali, with an average of 10.5 years' of practical experience and who were members of the Asociación Colombiana de Hematología y Oncología [Colombian Association of Hematology and Oncology].

Conclusions: the consensus established 26 considerations for the diagnosis and treatment of MCL, according to the Colombian context, aimed at healthcare professionals with a direct relationship with this disease. It is expected that clinical management will be homogenized by a consideration of this consensus and the referenced literature. **(Acta Med Colomb 2022; 48. DOI: https://doi.org/10.36104/amc.2023.2606).**

Keywords (DeCS): mantle cell lymphoma, treatment, chemotherapy, immunotherapy, nuclear medicine, radiation therapy.

Introduction

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy, with an incidence of 5-7 cases per 100,000 inhabitants worldwide, and a cumulative incidence of 544,352 in 2020 (1). To date, more than 40 subtypes with different morphological, clinical and genetic

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characteristics have been described, making it a diagnostic challenge in which appropriate and timely treatment affects the patient's prognosis (2).

Within these subtypes, mantle cell lymphoma (MCL), or what was previously known as intermediate lymphocytic lymphoma, accounts for 3-10% of B cell NHLs, is characterized by being aggressive and usually debuts in advanced stages (3-5). An incidence of one case per 200,000 inhabitants has been reported, which increases with age, and is more frequent in Caucasians, white Hispanics and, to a lesser extent, Asians, with an average age of onset between 60 and 70 years. It is more frequent in males, with a 3:1 male to female ratio, and has a median survival of 8-10 years (4, 6, 7). The clinical manifestations vary; however, lymph node (75%), bone marrow (60-80%), spleen (45-60%) and extranodal involvement (like the gastrointestinal tract, breast, pleura and orbit) have been reported (8-11). In addition, 33% of the patients have constitutional or B systemic symptoms like night sweats, weight loss and fever (12, 13).

Once the symptoms begin, the diagnosis is based on a lymph node or bone marrow biopsy. The histopathological study evaluates the cells' phenotypic characteristics, in which small or intermediate lymphocytes, notched nuclei and blastoid cells are generally found. However, they may have fine chromatin which mimics acute leukemia, and the proliferation index and mitosis may vary (7, 14). Mantle cell lymphoma may have two divisions, one known as "classic" which affects the lymph nodes and extranodal locations with a frequent expression of SOX11 and often non-mutated immunoglobulin heavy chains (IGHVs). The second or "leukemic" variant predominantly involves the blood and bone marrow, but with a generally negative SOX11 and hypermutated IGHV, and is more aggressive, with a poor prognosis (15, 16). The presence of immunohistochemichal markers like CD5, CD10, CD19, CD23, CD22 and CD25 has been reported, along with others like cyclin D1 expression. Genetic tests are considered part of the diagnostic process, with the most common being 11;14 translocation, which is found in 40-70% of the usual cytogenetic tests (karyotypes for leukemic states) and 95% of fluorescence *in situ* hybridization (FISH), with a lower frequency of other deletions like 11q22 and 13q14 (14, 17-19). In addition, diagnostic imaging has become an essential tool both for staging the involvement as well as determining the disease prognosis. Thus, positron emission tomography (PET/CT) plays a role today in the initial staging and follow up during treatment (20, 21). The Mantle International Prognostic Index (MIPI), developed by the Eastern Cooperative Oncology Group (ECOG), is another instrument for the initial classification which groups three risk stages: low risk (median survival of 60 months), intermediate risk (median survival of 50 months) and high risk (median survival of 29 months). Currently, the Ki-67 (cellular proliferation) marker is included as part of this scale; however, it is operator-dependent (14, 22, 23).

Treatment is oriented according to the patient's classification according to age, functional status and comorbidities, which are directly related to the ability to receive intensive treatment/transplantation. Immunochemotherapy is considered for initial therapy to be consolidated later with transplantation. The treatment options include protocols with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP), cyclophosphamide, vincristine, Adriamycin and dexamethasone (Hyper-CVAD) and bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP), among others. Their use depends on the MCL classification and patient characteristics (14, 24). After this, the treatment should be evaluated early on, reevaluating the patient's symptoms, complete blood count, lactate dehydrogenase (LDH) and inflammatory response markers, to indirectly visualize the disease's activity. Evaluation of the extranodal sites that initially showed involvement should also be considered, for instance with gastrointestinal tract endoscopy (25, 26). Finally, treatment consolidation culminates in transplantation for those with a partial or complete response. Transplantation may be autologous or allogeneic, with the choice determined by the pharmacological treatment received (27). One aspect that still causes debate is consolidation with radiation therapy, which suggests local control of the disease; however, a risk-benefit analysis is recommended in light of the side effects. These clinical interventions are currently being permeated by new treatments in which targeted therapy is now an option, with clinical studies showing its effectiveness in this type of patients.

This description of the approach to patients with MCL entails a series of both diagnostic and therapeutic challenges, which have led to a variety of alternatives with advantages and disadvantages, depending on the characteristics of the patient and the disease, which requires that the attending physicians use an appropriate approach and begin prompt, personalized treatment. These options are also tied to the availability of diagnostic resources at the different centers.

Thus, considering the relevance of this disease in terms of the patient's prognosis and care-related costs, it is important to consider standardizing the actions in order to offer the best alternatives within the Colombian context, as both diagnostic and treatment alternatives are available today, most of which are funded by the Colombian healthcare system. Consequently, the Asociación Colombiana de Hematología y Oncología (ACHO) [Colombian Association of Hematology and Oncology], which gathers a significant number of professionals involved in caring for MCL patients, has created spaces to guide real-life clinical activity. Therefore, expert multidisciplinary consensuses, like this one, have become an easily accessible and readable tool, stressing that these initiatives are not intended to replace the clinical practice guidelines, but rather present

the clinical experience with this disease in an exclusively Colombian context (28).

This expert consensus on MCL considered the current legislation and regulatory agency concerns regarding the availability of and access to the diagnostic and treatment options. It is important to mention that this project is a scientific-academic rather than a regulatory initiative. Finally, this document presents some suggested medications which, despite the availability of scientific evidence, are not approved by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA) [National Institute for Drug and Food Surveillance]. These could be considered so that in the future, once they are approved, they can be used according to the indications and clinical discretion of ACHO (29).

Thus, the objective of this project was to generate an expert consensus of recommendations for diagnosing and treating MCL based on the Colombian context.

Methods

The developing group reviewed the most representative literature including primary and secondary studies, such as pivotal studies, systematic reviews and practice guidelines used by clinical experts in their usual clinical practice. The development of the consensus is described below:

Procedure

The questions were based on the importance of standardizing clinical practice, evaluating the possibility of unifying actions based on experience and the context of the Colombian healthcare system. Likewise, the group developed the questions according to each specialty's role, to obtain a position from different perspectives. A scale from 1-9 was used to score the options for each question (1 was defined as the most inappropriate or what would not be done in clinical practice and 9 was the most appropriate or what would be done as a first line action) and the interquartile ranges (IQRs) were calculated to find the dispersion of the scores. Consensus was determined when the medians were between 1 and 3 with an IQR between 1 and 3, and when medians were 7-9 with an IQR between 7 and 9. Taking this procedure into account, a matrix was designed to consolidate and analyze the results. The questions and options were constructed in Google Forms to be sent remotely to the experts (Figure 1).

First round: as described, the developing group consisting of four hematologists sent the questionnaire, which was scored by the clinical experts, and the information was then consolidated and analyzed. The options with a consensus were identified and those without consensus were sent to a second round of scoring.

Second round: a matrix was constructed showing the first-round results, which also included comments made by the experts, as part of the score. This matrix was sent to the experts in masked form to provide feedback to the entire group of experts. The form containing the questions without consensus was sent at the same time in order to reevaluate the scores according to the feedback, hoping to reach a consensus. Once the second-round scores were received, the information was consolidated and whatever definitely did not reach a consensus was sent for discussion in the nominal consensus.

Nominal consensus: the group of developers invited the experts to an open plenary to discuss the questions and options which did not achieve consensus, in order to understand the different positions and reach a consensus. In this stage, consensus was achieved when 80% of the experts agreed on an action.

Results

Twenty-five questions for diagnosing and treating MCL were drafted and discussed, with 22 medical spe-

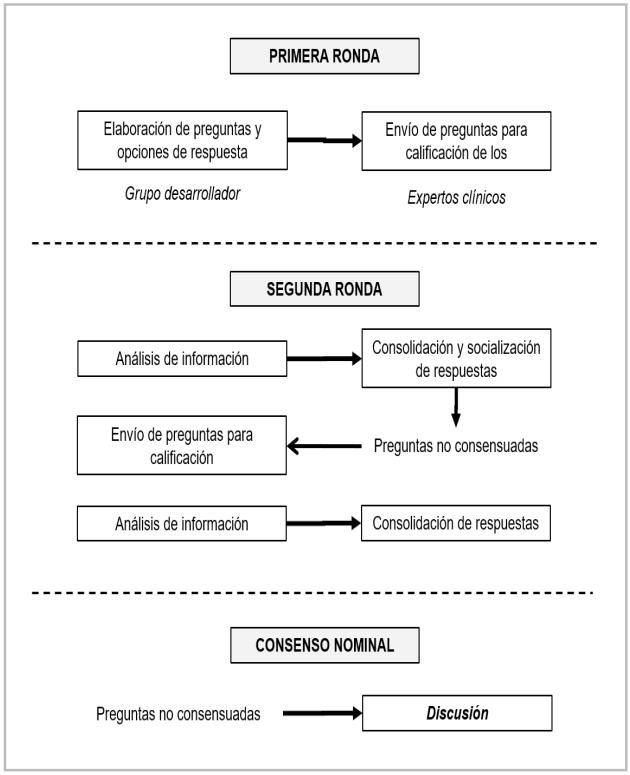

Figure 1. *Execution.*

cialists participating: 16 hematologists and hematologists-oncologists, four hematological pathologists, one radiation therapist and one nuclear medicine specialist, from Bogotá, Medellín and Cali, with a median clinical practice experience of 10.5 years, and members of ACHO.

Questions and Suggestions

1. What histopathological/cytogenetic studies are needed in MCL ?

The following diagnostic tests are suggested:

Immunohistochemistry for CD20, CD3, CD5, CD10, CD21, CD23, BCL2, BCL6, TP53, and Ki-67, including cyclin D1.

Immunohistochemistry for SOX11.

Flow cytometry cell surface marker analysis for kappa/lambda, CD19, CD20, CD5, CD23, and CD10.

Flow cytometry cell surface marker analysis for CD200.

FISH study for t(11;14).

It is important to consider LEF1 immunohistochemistry in the rare cases of MCL which could be confused with B-cell chronic lymphocytic leukemia (B-CLL), and in the blastoid or pleomorphic variants, as a differential diagnosis (13, 27, 30, 31).

2. Is a leukemia karyotype analysis considered a routine diagnostic test for determining the prognosis of patients with MCL

A leukemia karyotype is suggested, since it is available in the Colombian setting (32).

3. ?What additional studies are needed for appropriate risk stratification in MCL

The following diagnostic tests are suggested:

Analysis for TP53 mutation and/or 17P deletion.

Analysis for IGHV mutations (4, 6, 14, 30).

4. Should the circulating monoclonal component be evaluated?

This is not routinely suggested; however, it may be considered in patients with clinical criteria and MCL variants with a monoclonal component, as well as for the initial differential diagnosis.

5. Regarding full-body PET/CT at diagnosis:

The following is suggested:

Initial staging with PET/CT for ALL cases, especially at diagnosis, if radiation therapy or shortened systemic therapy is planned for treating stages I and II (early), as this may affect the radiation therapy prescription and length of treatment.

Ordering a PET/CT should not prevent beginning medical or surgical treatment, considering the time required to perform the test and receive the results, as well as its availability (13, 20, 21, 31, 33-36).

6. Regarding upper GI endoscopy and total colonoscopy with a biopsy and sedation:

This is always suggested in ALL cases at diagnosis, and is especially important in stages I and II, when there are gastrointestinal symptoms and/or when there is gastrointestinal bleeding.

This suggestion was agreed upon by the participating experts based on their experience, coinciding in the perception of a greater prevalence of possible gastrointestinal involvement in this type of lymphoma in our country. This is why it is recommended for ALL cases, as long as there is access to endoscopic studies, keeping in mind that PET/CT is not available in some geographical areas. However, according to the NCCN guidelines, this varies according to the epidemiological and access situation in some regions of Colombia (12, 13, 27, 37).

7. Regarding bone marrow aspiration/biopsy studies

These are recommended for all cases at diagnosis, especially for stages I and II with hematological involvement found on the complete blood count (13, 27, 38).

8. Regarding lumbar puncture for cerebrospinal fluid (CSF) studies (like cytochemistry, cytology, and flow cytometry in a TransFix tube)

The recommendation is:

For patients with a risk of central nervous system involvement (blast variant with central nervous system symptoms, proximity to the central nervous system, involvement of the ocular adnexa, kidney involvement and elevated LDH)

It may be considered in other cases, according to clinical judgement and the availability of diagnostic tests (12, 14, 27).

9. Regarding imaging assessment of the treatment response

It is suggested that:

Full-body PET/CT be considered for the final evaluation of treatment in all cases.

Chest, abdominal and pelvic tomography with contrast should be considered for ALL cases in which they are not contraindicated, if PET/CT is not performed.

Routine full-body PET/CT is not suggested for intermediate evaluation during treatment. However, it may be considered in those who had a positive initial PET/CT, and to evaluate extranodal involvement.

It is important to mention that ordering a PET/CT should not be an impediment to continuing medical or surgical treatment, considering the time required for it to be performed and have results delivered, as well as its availability (13, 20, 21, 31, 33-36).

10. Regarding repeating the biopsy and analysis of the TP53 mutation/17P deletion:

It is suggested:
For symptom progression or the onset of indications for treatment of the indolent type.
For all cases of nonresponse or relapse (27).

11. What First line treatment options do you consider for patients with early MCL disease (Stage I/II non-bulky) ?

The following is suggested:
Shortened chemo-immunotherapy, consolidated with radiation therapy.
In localized disease, in those in whom chemotherapy cannot be used or for patients who prefer not to use chemotherapy (unsuitable for systemic treatment), exclusive radiation therapy may be considered as an option (27, 39).

12. If using chemo-immunotherapy, which first line treatment protocol would you consider for patients with early MCL disease (Stage I/II non-bulky)?

The following are suggested:
R-CHOP.
R – Bendamustine is considered to be a treatment option; however, it does not have INVIMA registration at the moment, despite evidence of its use.
VcR-CAP is considered as a treatment option in Stage II (according to clinical judgment). It is not suggested in Stage I and shortened regimens.

The following is not suggested:
Rituximab + lenalidomide (27).

13. What first line treatment options would you consider for patients with advanced aggressive MCL (II Bulky - Stages III and IV) who are candidates for transplantation - intensive treatment? ?

The following are suggested:
Alternating R-DHAP / R-CHOP.
R – DHAP.
Hyper-CVAD.
NORDIC regimen: Maxi-CHOP.

The following are not suggested:
R-CHOP.
VcR – CAP.
R – Bendamustine (27).

14. What first line treatment options would you consider for patients with a diagnosis of asymptomatic indolent MCL?

Suggested:
Observation.

Not suggested:
A reduced intensity chemotherapy regimen (13, 27).

15. What first line treatment options would you consider for patients diagnosed with asymptomatic indolent MCL with an indication for treatment who are candidates for transplantation - intensive treatment ?

The following are suggested as treatment options:
Modified hyper-CVAD.
Alternating R-DHAP / R-CHOP.
R – DHAP.
Hyper-CVAD.
NORDIC regimen: Maxi-CHOP.

In the event that one of the previous options is not indicated or is contraindicated, the following is suggested:
Bendamustine + rituximab.

It is important to keep the patient's comorbidities and tp53 mutation in mind.

The following is not suggested:
Rituximab – lenalidomide.
VcR-CAP.

It is important to consider that indolent is defined as: not rapidly progressive, without blastoid morphology, patients with negative SOX11 and p53 biomarkers, mutated IGHV, a clinical presentation similar to non-nodal CLL, having splenomegaly, a low tumor burden and Ki-67 <30% (13, 27, 40, 42).

16. What first line treatment options would you consider for patients diagnosed with asymptomatic indolent MCL who are not candidates for transplantation or intensive treatment?

Suggested:
R-CHOP.
R- Bendamustine.
VcR-CAP
Rituximab + bendamustine + citarabine (R-BAC 500).

Not suggested:
Rituximab – lenalidomide.
Observation (13, 27, 40, 41).

17. In which patients is radiation therapy indicated ?

Suggested in:
Bulky disease, in patients who have finished chemo-immunotherapy and have it indicated as consolidation.
Localized disease.
Patients with a partial response, who are not candidates for transplantation.
- It should be kept in mind that in cases where the patients do not respond to their first line and are not candidates for transplantation, the biopsy should be repeated and a second line of rescue treatment should be started (27, 39).

18. Should consolidation with autologous hematopoietic stem cell transplantation be done at the first referral in eligible patients?

Consolidation with autologous hematopoietic stem cell transplantation is suggested at the first referral of fit patients (13, 27).

19. Should maintenance strategies be used in MCL patients over the age of 18 with complete response to the initial treatment?

Maintenance strategies are suggested in MCL patients over the age of 18 with complete response to the initial treatment.

It is important to mention that maintenance applies both to cases that undergo high-dose therapy and autologous hematopoietic stem cell transplantation (AHSCT) after this complete treatment response as well as those that do not undergo AHSCT, especially if the R-CHOP regimen was their initial treatment (27).

20. What treatment is recommended for maintenance in patients with MCL?

Suggested:
Rituximab in patients who had a complete response.

Not suggested:
Observation, except in indolent MCL (13, 27).

21. What MCL treatment options would you consider in patients with central nervous system involvement?

Suggested:
Intrathecal chemotherapy.
High-dose methotrexate.
Palliative radiation therapy in patients with no other treatment option (27, 39, 43).

22. What rescue treatment would you consider in patients FIT for intensive treatment with a confirmed MCL diagnosis on their first relapse?

Suggested:
Ibrutinib.
R-DHAP, if it was not used as first line treatment.
Rituximab – ifosfamide, cytarabine, etoposide (R-ICE).
RBAC-500 in patients with late relapse and in good clinical condition.
R-Bendamustine.
Rituximab – gemcitabine, oxaliplatin (R-GEMOX).
- It is important to mention that this should not be considered for first line intensive consolidation treatment.

In patients who are to undergo allogeneic transplant or a second autologous transplant, more intensive regimens should be considered for rescue, according to the patient's clinical condition.

Not suggested:
- Rituximab + lenalidomide
- R-CHOP (27, 44-46).

23. What rescue treatment options would you consider for patients with a confirmed MCL diagnosis who are NOT FIT for intensive treatment, on their first relapse?

Suggested:
Ibrutinib.
R-bendamustine.

Not suggested:
R-DHAP.
R-ICE.
R-GEMOX.
R-CHOP (27, 45, 47).

24. What is the role of Allogeneic hematopoietic stem cell transplantation in patients in second remission?

Allogeneic hematopoietic stem cell transplantation can be considered for eligible patients in second remission (27, 48-50).

Glossary

- **IGHV**: immunoglobulin heavy variable
- **PET/CT**: positron emission tomography /computed tomography
- **R-CHOP**: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
- **R-Bendamustine**: rituximab - bendamustine
- **VcR-CAP**: rituximab, cyclophosphamide, doxorubicin, bortezomib, and prednisone
- **R-DHAP**: rituximab, dexamethasone, cytarabine and cisplatin
- **Hyper-CVAD**: cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine
- **MaxiCHOP**: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
- **R-BAC 500**: rituximab, bendamustine and cytarabine,
- **R-ICE**: rituximab, ifosfamide, carboplatin and etoposide
- **R-GEMOX**: rituximab, gemcitabine and oxaliplatin

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References

1. **GLOBOCAN.** Non-Hodgkin lymphoma. EE.UU. 2020 [Disponible en: https://gco.iarc.fr/today/data/factsheets/cancers/34-Non-hodgkin-lymphoma-fact-sheet.pdf.
2. **Chihara D, Nastoupil LJ, Williams JN, Lee P, Koff JL, Flowers CR**. New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy. *Expert Rev Anticancer Ther.* 2015;**15(5):**531-44.
3. **J. Enciso L, L. Suarez M, Arango M**. Resultados del tratamiento del linfoma de células del manto con varios regímenes de inmunoquimioterapia: estudio retrospectivo. *Revista Colombiana de Cancerología*. 2015;**19(2):**71-81.
4. **Jain P, Wang M.** Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. *Am J Hematol*. 2019;**94(6):**710-25.
5. **Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al.** World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;**17(12):**3835-49.
6. Wang Y, Ma S. Racial differences in mantle cell lymphoma in the United States. *BMC Cancer.* 2014;**14:**764.
7. **Lynch DT, Acharya U.** Mantle Cell Lymphoma. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
8. **Yoon DH, Cao J, Chen TY, Izutsu K, Kim SJ, Kwong YL, et al.** Treatment of mantle cell lymphoma in Asia: a consensus paper from the Asian Lymphoma Study Group. *J Hematol Oncol*. 2020;**13(1):**21.
9. **Argatoff LH, Connors JM, Klasa RJ, Horsman DE, Gascoyne RD.** Mantle cell lymphoma: a clinicopathologic study of 80 cases. *Blood*. 1997;**89(6):**2067-78.
10. **Romaguera JE, Medeiros LJ, Hagemeister FB, Fayad LE, Rodriguez MA, Pro B, et al.** Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer*. 2003;**97(3):**586-91.
11. **Ferrer A, Salaverria I, Bosch F, Villamor N, Rozman M, Beà S, et al.** Leukemic involvement is a common feature in mantle cell lymphoma. *Cancer*. 2007;**109(12):**2473-80.
12. **Freedman AS, Lister AJ, Rosmarin A.** Clinical manifestations, pathologic features, and diagnosis of mantle cell lymphoma. 2021 [Disponible en https://www-uptodate-com.fucsalud.basesdedatosezproxy.com/contents/clinical-manifestations-pathologic-features-and-diagnosis-of-mantle-cell-lymphoma?search=Mantle%20cell%20lymphoma&source=search_result&selectedTitle=1~89&usage_type=default&display_rank=1.
13. **Instituto Nacional de Cancerología.** Guía de práctica clínica para la detección, tratamiento y seguimiento de linfomas Hodgkin y No Hodgkin en población mayor de 18 años. Colombia 2017 [Disponible en: https://intranet.cancer.gov.co/Guias_y_%20Protocolos/GUIAS/linfomas_Hodgkin_y_No_Hodgkin/GPC_profesionales_de_la_salud.pdf.
14. **Navarro Matilla B, García-Marco JA.** Linfoma de células del manto: ¿hacia una estrategia terapéutica individualizada? *Medicina Clínica*. 2015;**144(12):**553-9.
15. **Vegliante MC, Palomero J, Pérez-Galán P, Roué G, Castellano G, Navarro A, et al.** SOX11 regulates PAX5 expression and blocks terminal B-cell differentiation in aggressive mantle cell lymphoma. *Blood*. 2013;**121(12):**2175-85.
16. **Maddocks K**. Update on mantle cell lymphoma. *Blood*. 2018;**132(16):**1647-56.
17. **Dorfman DM, Pinkus GS.** Distinction between small lymphocytic and mantle cell lymphoma by immunoreactivity for CD23. *Mod Pathol*. 1994;**7(3):**326-31.
18. **Bosch F, López-Guillermo A, Campo E, Ribera JM, Conde E, Piris MA, et al.** Mantle cell lymphoma: presenting features, response to therapy, and prognostic factors. *Cancer*. 1998;**82(3):**567-75.
19. **DiRaimondo F, Albitar M, Huh Y, O'Brien S, Montillo M, Tedeschi A, et al**. The clinical and diagnostic relevance of CD23 expression in the chronic lymphoproliferative disease. *Cancer*. 2002;**94(6):**1721-30.
20. **Yang S, Fu L, AbuduRxiti M, Wu J, Wang Q, Qin Y, et al.** Application of 18F-fluorodeoxyglucose positron emission tomography/computerized tomography in mantle cell lymphoma. *Nucl Med Commun*. 2020;**41(5):**477-84.
21. **Albano D, Ferro P, Bosio G, Fallanca F, Re A, Tucci A, et al.** Diagnostic and Clinical Impact of Staging (18)F-FDG PET/CT in Mantle-Cell Lymphoma: A Two-Center Experience. *Clin Lymphoma Myeloma Leuk*. 2019;**19(8):**e457-e64.
22. **Geisler CH, Kolstad A, Laurell A, Räty R, Jerkeman M, Eriksson M, et al.** The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). *Blood*. 2010;**115(8):**1530-3.
23. **Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al.** A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008;**111(2):**558-65.
24. **Klener P.** Advances in Molecular Biology and Targeted Therapy of Mantle Cell Lymphoma. *Int J Mol Sci*. 2019;**20(18).**
25. **Hosein PJ, Pastorini VH, Paes FM, Eber D, Chapman JR, Serafini AN, et al.** Utility of positron emission tomography scans in mantle cell lymphoma. *Am J Hematol*. 2011;**86(10):**841-5.
26. **Seam P, Juweid ME, Cheson BD.** The role of FDG-PET scans in patients with lymphoma. *Blood*. 2007;**110(10):**3507-16.
27. Oncology. Non-Hodgkin´s Lymphoma Version 3.2021 EE.UU. 2021 [Disponible en: https://wwwnccn.org/nccn/guideline/hematologic/nhl/english/foll.pdf.
28. **Ospina AV, Contreras F, Yepes A, Lehmann C, Bobadilla IA, Lema M, et al.** Diagnóstico y tratamiento multidisciplinario de melanoma temprano y localmente avanzado. Consenso de expertos. Asociación Colombiana de Hemato-Oncología (ACHO). *Rev Col Can*. 2021;**25(2):**1-10.
29. **Ospina AV, Brugés R, Lema M, De Lima Lopes Jr. G, Gómez G, Lombana M, et al.** Tratamiento de cáncer de pulmón metastásico (estadio IV) de célula no pequeña. Consenso de expertos, Asociación Colombiana de Hematología y Oncología (ACHO). *Rev Col Hem Onc*. 2018;**5(1):**61-71.
30. **Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al.** The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;**127(20):**2375-90.
31. **Bodet-Milin C, Touzeau C, Leux C, Sahin M, Moreau A, Maisonneuve H, et al.** Prognostic impact of 18F-fluoro-deoxyglucose positron emission tomography in untreated mantle cell lymphoma: a retrospective study from the GOELAMS group. *Eur J Nucl Med Mol Imaging*. 2010;**37(9):**1633-42.
32. **Greenwell IB, Staton AD, Lee MJ, Switchenko JM, Saxe DF, Maly JJ, et al.** Complex karyotype in patients with mantle cell lymphoma predicts inferior survival and poor response to intensive induction therapy. *Cancer*. 2018;**124(11):**2306-15.
33. **Albano D, Laudicella R, Ferro P, Allocca M, Abenavoli E, Buschiazzo A, et al.** The Role of 18F-FDG PET/CT in Staging and Prognostication of Mantle Cell

Lymphoma: An Italian Multicentric Study. *Cancers (Basel)*. 2019;**11(12).**

34. **Albano D, Treglia G, Gazzilli M, Cerudelli E, Giubbini R, Bertagna F.** (18) F-FDG PET or PET/CT in Mantle Cell Lymphoma. *Clin Lymphoma Myeloma Leuk*. 2020;**20(7):**422-30.
35. **Alavi A, Shrikanthan S, Aydin A, Talanow R, Schuster S.** Fluorodeoxyglucose-positron-emission tomography findings in mantle cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2011;**11(3):**261-6.
36. **Jeon YW, O JH, Park KS, Min GJ, Park SS, Yoon JH, et al**. Prognostic impact of interim positron emission tomography in mantle cell lymphoma patients treated with frontline R-CHOP. *Br J Haematol*. 2020;**188(6):**860-71.
37. **Iwamuro M, Okada H, Kawahara Y, Shinagawa K, Morito T, Yoshino T, et al.** Endoscopic features and prognoses of mantle cell lymphoma with gastrointestinal involvement. *World J Gastroenterol*. 2010;**16(37):**4661-9.
38. **Clement PW, Salama ME.** Early bone marrow involvement by mantle cell lymphoma. *Blood*. 2015;**126(6):**825.
39. **Ben Barouch S, Kuruvilla J, Tsang RW, Yashphe E, Sarid N.** Radiotherapy in mantle cell lymphoma: A literature review. *Hematol Oncol*. 2020;**38(3):**223-8.
40. **Flinn IW, van der Jagt R, Kahl B, Wood P, Hawkins T, MacDonald D, et al**. First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *J Clin Oncol*. 2019;**37(12):**984-91.
41. **Martin P, Ghione P, Dreyling M.** Mantle cell lymphoma - Current standards of care and future directions. *Cancer Treat Rev*. 2017;**58:**51-60.
42. **Aukland P, Lando M, Vilholm O, Christiansen EB, Beier CP**. Predictive value of the Status Epilepticus Severity Score (STESS) and its components for long-term survival. *BMC Neurol*. 2016;**16(1):**213.
43. **Cheah CY, George A, Giné E, Chiappella A, Kluin-Nelemans HC, Jurczak W, et al.** Central nervous system involvement in mantle cell lymphoma: clinical features, prognostic factors and outcomes from the European Mantle Cell Lymphoma Network. *Ann Oncol*. 2013;**24(8):**2119-23.
44. **McCulloch R, Visco C, Eyre TA, Frewin R, Phillips N, Tucker DL, et al.** Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *Br J Haematol*. 2020;**189(4):**684-8.
45. **Merryman RW, Edwin N, Redd R, Bsat J, Chase M, LaCasce A, et al.** Rituximab/bendamustine and rituximab/cytarabine induction therapy for transplant-eligible mantle cell lymphoma. *Blood Adv*. 2020;**4(5):**858-67.
46. **Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Geisler CH, Trneny M, et al**. Treatment of Older Patients With Mantle Cell Lymphoma (MCL): Long-Term Follow-Up of the Randomized European MCL Elderly Trial. *J Clin Oncol*. 2020;**38(3):**248-56.
47. **Le Gouill S, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Dartigeas C, et al.** Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *N Engl J Med*. 2017;**377(13):**1250-60.
48. **Robak T, Smolewski P, Robak P, Dreyling M.** Mantle cell lymphoma: therapeutic options in transplant-ineligible patients. *Leuk Lymphoma*. 2019;**60(11):**2622-34.
49. **Hanel W, Epperla N.** Emerging therapies in mantle cell lymphoma. *J Hematol Oncol*. 2020;**13(1):**79.
50. **Sawalha Y, Radivoyevitch T, Tullio K, Dean RM, Pohlman B, Hill BT, et al.** The Role of Upfront Autologous Hematopoietic Cell Transplantation in the Treatment of Mantle Cell Lymphoma, a Population Based Study Using the National Cancer Data Base (NCDB). *Blood*. 2017;**130(Supplement 1):**2009.