MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

JOÃO PEDRO DE OLIVEIRA PIMENTA

Factors influencing therapeutic response in Mantle cell lymphoma

ARTIGO CIENTÍFICO ORIGINAL
ÁREA CIENTÍFICA DE HEMATOLOGIA

Trabalho realizado sob a orientação de:

PROFESSORA DOUTORA ANA BELA SARMENTO ANTUNES CRUZ RIBEIRO
PROFESSORA DOUTORA CATARINA ISABEL BATISTA GERALDES DOS SANTOS

ABRIL/2021

Título

Factors influencing therapeutic response in Mantle cell lymphoma.

Autores

João Pedro De Oliveira Pimenta (1), Catarina Geraldes (2) (3), Ana Bela Sarmento (2)(3)

Afiliações

(1) Estudante do 6º ano do Mestrado Integrado em Medicina da Faculdade de Medicina, Universidade de Coimbra, Coimbra 3000-548, Portugal;

(2) Serviço de Hematologia Clínica, Centro Hospitalar e Universitário de Coimbra, Coimbra 3000-075, Portugal;

(3) Centro de investigação em Meio ambiente genética e Oncobiologia. Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal.

Endereço do autor correspondente

Ana Bela Sarmento

Serviço de Hematologia Clínica, Centro Hospitalar e Universitário de Coimbra, Coimbra 3000-075, Portugal;

absarmento@fmed.uc.pt

Abstract

Background: Mantle cell lymphoma is a rare subtype of non-Hogdkin lymphoma thatis still considered incurable. Only about half of the patients are fully responsive to the firsttherapeutic line and the determinant factors are still unknown.

Aim: To determine if there are statistically relevant factors influencing the complete response to treatment.

Methods: In this cross-sectional study, patients diagnosed and treated in Centro Hospitalar Universitário de Coimbra with known response to first-line therapy were selected, gathering a total of 42 patients. To study the factors that influence treatment response, pa-tients were split according to multiple variables such as age, gender, or their performancestatus. The average response rate of each one was then compared using Aspin-Welch t-test.

Results: Patients under the age of 65 years present better treatment response (87.5% complete response rate) when compared to older patients (46.2%) displaying a divergence of more than 40%.

Conclusion: In our cohort, age under 65 years old is the only factor determining abetter response to first-line treatment.

Keywords: Mantle cell lymphoma, cyclin d, diagnosis, therapy, prognosis

Resumo

Introdução: O linfoma de células do manto é um subtipo raro de linfoma não-Hogdkin que ainda é considerado incurável. Apenas metade dos doentes entram em remissão completa com a primeira linha terapêutica e os factores influentes são ainda desconhecidos.

Objetivo: Determinar se existem factores estatisticamente relevantes que influenciem a resposta completa ao tratamento.

Métodos: Neste estudo transversal, foram seleccionados os doentes diagnosticados e tratados no Centro Hospitalar Universitario de Coimbra com resposta conhecida à terapêutica de primeira linha, reunindo um total de 42 doentes. Para estudar os factores que influenciam a resposta ao tratamento, os doentes foram divididos de acordo com múltiplas variáveis tais como idade, sexo ou score ECOG. A taxa média de resposta de cada um foi então comparada utilizando o teste Aspin-Welch.

Resultados: Os doentes com idade inferior a 65 anos apresentam uma melhor respostaao tratamento (87,5% de taxa de resposta completa) quando comparados com os doentes mais velhos (46,2%), com uma diferença de mais de 40%.

Conclusão: A idade inferior a 65 anos é o único factor determinante de uma melhor resposta ao tratamento de primeira linha.

Palavras-chave: Linfoma de células do manto, ciclina d, diagnóstico, tratamento, prognóstico

Abbreviation's list

- ARA-C:Cytosine arabinoside
- ASCT:Autologous stem cell transplant
- BR:Bendamustine rituximab
- BTK:Brutons tyrosine kinase
- CT:Computerized tomography
- ECOG:Eastern Cooperative Oncology Group
- FDG-PET: Fluorodeoxyglucose positron emission tomography
- FLIPI: Follicularlar Lymphoma International Prognostic Index
- FDA:Food and Drug Administration
- Hyper-CVAD:High dose of fractionated cyclophosphamide, vincristine,doxorubicin and dexamethasone
- IGHV- Immunoglobulin heavy chain
- IPI-International Prognostic Index
- LDH-Lactate dehydrogenase
- MCL:Mantle Cell Lymphoma
- MIPI:Mantle Cell Lymphoma International Prognostic Index
- NHL:Non-Hodgkin Lymphoma
- OS:Overall survival
- R-BAC:Rituximab,Bendamustine and Cytarabine
- R-CHOP: Rituximab,cyclosphophamide,Doxorubicin Hydrochloride(Hydroxydaunomycin), Vincristine Sulfate (Oncovin), Prednisone
- R-DHAP:Rituximab, dexamethasone,cytarabine, cisplatin
- WHO:World Health Organization

1 Introduction

1.1 General information on lymphomas

Lymphomas are a large group of malignancies that develop from lymphocytes development/differentiation with a very diverse clinical presentation and a quite heterogeneous response to treatment.

In the 2016 WHO classification of lymphoid neoplasms, lymphomas are categorized in 2 major groups: those derived from mature lymphoid cells and those derived from precursor lymphoid cells. It is possible to split these groups even further into B-cell and T-cell neoplasms.

1.2 Mantle cell lymphoma

Classically considered an incurable disease developed from naive B cells, mantle cell lymphomas (MCL) are a relatively uncommon subtype of non-Hodgkin lymphoma (NHL) (accounting for approximately 5% of all non-Hodgkin's lymphomas in North America and Europe [1]). With a median age at presentation of 67 years and with a higher incidence in Caucasians[7,8], MCL is characterized by the translocation t(11;14) (q13;q32) that causes an important cyclin D1 overexpression. The majority of patients present bone marrow involvement and, therefore, peripheral blood abnormalities are frequently found, such as lymphocytosis (around30% of patients) or cytopenias, negatively influencing the prognosis. [9,10] Once considered an aggressive lymphoma justifying aggressive and early therapy, MCL is now known to be a disease with a wide variety of clinical presentations, risk factors, and therapeutic management.Despite all this new biological knowledge and understanding about this pathology and the factthat survival rates have increased with the introduction of more targeted therapies, it is still a disease with a poor prognosis.

1.3 Disease classification

The 2016 revision of the World Health Organization classification of lymphoid neoplasms identified that MCL develops through two very different pathways as seen in Figure 1.

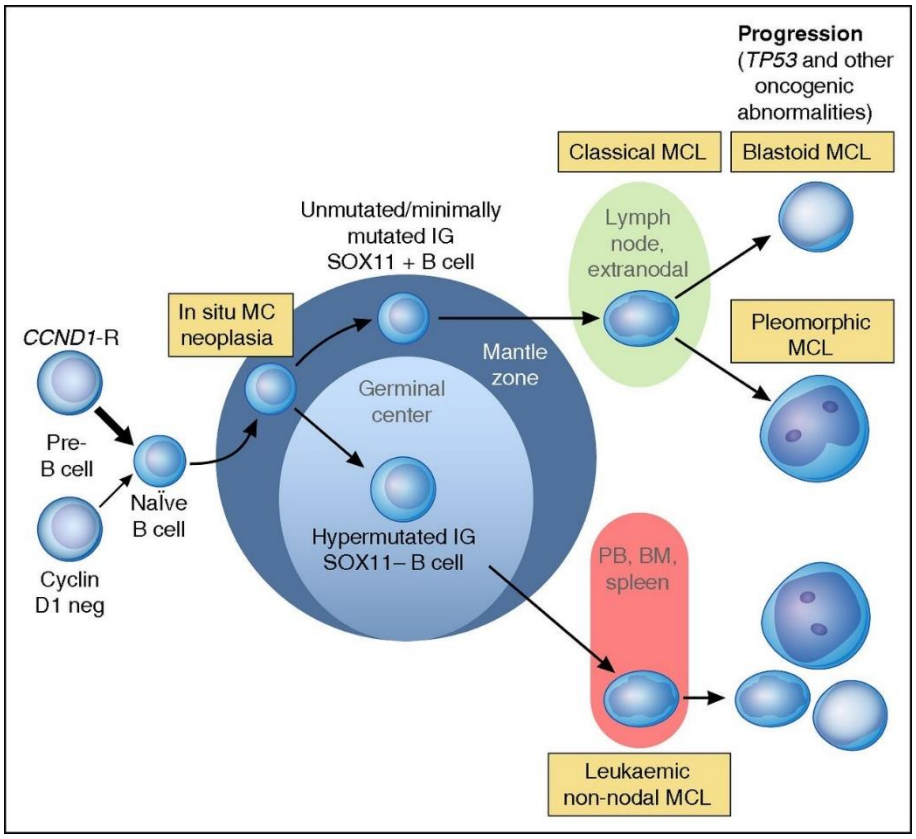

Figure 1: Hypothetical models of major mantle cell lymphoma (MCL) subtypes. Adapted from A Jareset al[3] and Swerdlow et al.[2]

Classic MCL is characterized by a SOX11 positive cells with a variable region of the immunoglobulinheavy chain (IGHV) with few or no mutations. It frequently presents itself with lymph nodes involvement. In some patients, some cytogenetic and molecular changes can occur leading to amore aggressive disease, called blastoid MCL or pleomorphic MCL, depending on its characteristics. The 2016 WHO revision presented a new variant of MCL, resulting from a combinationof mutated IGHV and SOX11 negative B cells. It typically affects the peripheral blood, bone marrow and spleen and has therefore been classified as leukemic nonnodal MCL.

Often it has a more indolent clinical course than the classic variant, although it can present itself as a very aggressive disease due to changes in TP53. In situ MCL neoplasia (formerly in situ MCL) mustbe distinguished from other forms of MCL and it is characterized by cyclin D1 positive cellsin the inner mantle zones. It is often detected in non-characteristic MCL lymphoid tissues, andtherefore mostly diagnosed when studying other lymphomas. [2]

1.4 Risk factors

Discussion still persists on the risk factors for MCL. Chronic infections, immune-deregulation, pesticide and fertilizer exposure, insecticide use, smoking and a high fat diet have been linked to an increase in NHL incidence. However, despite these initial studies, there is still no scientific evidence strong enough to assess meaningful risk factors that may predict the increasedincidence of this pathology in certain populations. [4,5]

1.5 Diagnosis

The diagnosis of MCL is established with a biopsy of a lymph node, bone marrow or other tissues or by blood immunophenotyping. Usually small to medium sized lymphoid cells with the typical mono-morphic morphology and irregular nuclear contours are observed. [6] Immunophenotyping is routinely used in the study of MCL in order to identify cells that are positive for CD5, CD19, CD20, CD22, CD201, CD51, BCL-2 and cyclin D1 and negative for CD10, CD23and BCL-6. The chromosomal translocation typically associated with MCL is t(11:14) (q13; 32) which leads to cyclin D1 overexpression in lymphocytes, unusual in normal lymphocytes. [7] However, some MCL have been detected that were classified as cyclin D1 negative and had not(11:14) (q13; 32) translocation associated. The SOX 11 transcription factor expression was found in most of these cells and can therefore be used as a specific biomarker for the diagnosis of this subgroup of cyclin D1 negative MCL. [8] There is a strong

association between the absence of SOX 11 expression and a more indolent evolution of the disease.[9] More aggressive subtypes like the blastoid variants are associated with altered biological factors such as a high ki-67 proliferative index or mutations in the p53 gene. [10] A generalized study of the patients has to be performed with complete blood count, biochemical study, LDH measurement and bone marrow evaluation. Flow cytometry immunophenotyping should be done on both bone marrow and peripheral blood. Imaging studies should also be performed and must include a cervico-thoraco-abdomino-pelvic computed tomography (CT) or FDG-PET/CT. More specific exams, for instance, an upper or lower digestive endoscopy or a cerebrospinal fluid evaluation should be performed if the patient has symptoms suggesting gastrointestinal orCNS involvement or if the previous studies report a more aggressive variant. [6]

1.6 Staging

The Ann Arbor staging system is, to date, the best available staging method. Classically a pure anatomic division, this classification created 4 stages of disease depending on the number of involved sites and if whether the disease is present above and/or below the diaphragm muscle. Later, this system was modified to include the presence or absence of systemic symptoms and classified patients as A, without B symptoms or B if B symptoms are present. However, it is recognized that Ann Arbor staging does not stratify patients into clinically useful groups, given that, at the end of the complete study, nearly all patients are staged as III or IV disease stage. Together with the recognition that other factors are important in predicting treatment outcome, some more relevant risk stratification tools were developed, such as the International Prognostic Index (IPI).

1.7 Prognostic factors and risk stratification

The International Prognostic Index (IPI) was originally designed to stratify the risk of B-cell non-Hodgkin lymphoma patients. This index was also used for MCL patients, but it was not very suitable, markedly in lower risk patients. There was a need to create a more specific prognostic index for this pathology. A new mantle cell lymphoma-specific prognostic index, the Mantle Cell International Prognostic Index (MIPI), was developed in 2008. The factors that independently influenced survival in a negative way included age above 65 years old, worse Eastern Cooperative Oncology Group (ECOG) performance status, higher LDH values and an elevated white blood cell count.[11, 12] With this new prognostic index, patients were stratified into three different prognostic groups: low-risk MIPI with the median overall survival (OS) not reached (5-year OS 60%), intermediate-risk MIPI with a median survival of 51 months, and high-risk MIPI with a median survival of 29 months. (Figure2)

1.8 Current and emerging treatment strategies

1.8.1 Observation

Patients are usually treated at diagnosis for disease-related symptoms or a rapid disease progression. With the better understanding of the disease pathology and the identification of less aggressive subtypes, it is recognized that some patients may benefit from the" watch and wait"strategy. Patients with non-nodal presentation, who are asymptomatic on diagnosis and patientswith low risk MIPI *scores* are candidates for a more conservative approach. It is estimated thatabout 5% of the MCL patients benefit from the deferral of therapy with no impact on their median survival. [14] Some studies go further to suggest that, in a small selected group of patients,the postponement of therapy is associated with better median overall survival rates. [15,16]

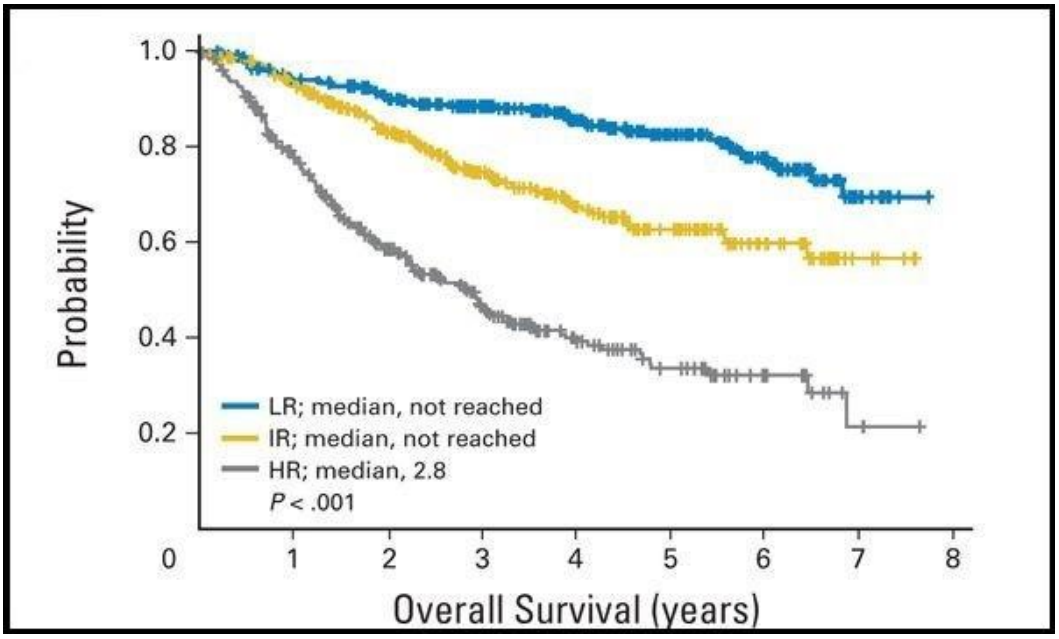

Figure 2: Overall survival by risk group in MCL. Kaplan-Meier analysis of overall survival in mantle cell lymphoma by MIPI risk group. (Adapted From Hoster et al.) [13]

LR: Low risk (upper curve), IR: Intermediate risk (middle curve), HR: High-Risk (lower curve)

1.8.2 First line therapy

Patients with mantle cell lymphoma may present remission after a wide range of common conventional chemotherapy regimens, although short-term full remissions are achieved in onlyabout half of the patients. The choice of therapy is dictated by the age and fitness of the patient.For example, the initial management of a young symptomatic patient often involves the useof a more aggressive therapy as early as possible. The median duration of remission in mostprevious trials was 1.5–3 years and the median OS was 3–6 years with standard chemotherapy.One of the first studies with significant results was from the European MCL Network [17], studied patients younger than 65 years who underwent myeloablative radiochemotherapy followed by autologous stem cell transplantation (ASCT) or alpha-interferon maintenance therapy(IFNα). The ASCT group achieved better results than the IFN group (3-year overall survivalwas 83% and 77% respectively. Later studies have shown that

induction therapy with a high dose of fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone(hyper-CVAD) alternating every 21 days with rituximab, plus a high-dose of cytarabine andmethotrexate for a total of 6 to 8 cycles, have a better 3-year failure-free survival rate of 52% andOS of 68%. However, these results come at the expense of a greater, but expected toxicity thanolder therapies. [18] Due to the difficulty of administering this alternating therapy, other alter-natives have been proposed with the disuse of one or more components of the therapy, namely ofmethotrexate. [19] Other studies suggest that methotrexate can be used as maintenance therapyand not as induction therapy without significant increase in toxicity. [20] The latest indicationsrecommend the use of induction therapy with a dose-intensified immunochemotherapy with R-CHOP + R-high dose ARA-C regimen, followed by an ASCT with rituximab as a maintenanceagent in younger patients. [21].

Patients ineligible for intensive therapy or bone marrow transplantation represent the larger patient population of MCL. This population requires a deeper consideration in aggressive therapy and usually the first line choice is conventional immunochemotherapy with R-CHOP, VR-CAP or R-BAC. Rituximab is used for maintenance as well. One of the most recent studies [22] shows that that switching from vincristine to bortezomib in R-CHOP therapy significantly improved median overall survival in MCL patients with a workable safety profile. The 4-year overall survival estimated with VR-CAP was 64% compared with 54% with R-CHOP.

1.8.3 Relapsed disease

When a relapse is suspected, a biopsy should be performed again in order to confirm relapse and to identify prognostic features of MCL. Patients remaining asymptomatic may benefit from more conservative measures and a number of these patients do not need treatment for months or even years. When patients present symptoms associated with relapse of the disease, several therapeutic options can be offered. If an early relapse ($\leq$ 24 months since treatment) is detected,

a non-cross-resistant scheme should be the choice, such as Bendamustine rituximab (BR) or Rituximab, Bendamustine and Cytarabine (R-BAC). Because the usual therapies for treating MCL have limited results in the relapsed disease, compounds targeting known signaling pathways must be strongly considered if there is no contraindication for this therapy. Recently, the oral covalent inhibitor of Bruton's tyrosine kinase BTK Ibrutinib (PCI-32765) was approved by the Food and Drug Administration (FDA) for the treatment of relapsed MCL. Due to its high response rate and long-term remissions, this therapy has been gaining relevance in the treatmentflowchart of this disease. However, early relapses to this therapy regularly present with very aggressive disease. [23, 21]

2. Methods

2.1 Study Design

The aim of the study was to study both patient and tumor characteristics that may influence treatment response. To accomplish the aim of our study, a cross sectional study was designed to analyze the impact of several variables separately and together on the response to first-line therapies of MCL. Ethical approval for the study was obtained from the Faculty of Medicine, University of Coimbra (FMUC) ethical Commission. Informed consent was not required for this type of retrospective analysis.

2.2 Selection of Patients

Patients selected for this study were all diagnosed and treated for MCL in CHUC between February 2008 and November 2020. A total of 54 patients met the criteria for diagnosis of MCL. The study inclusion criteria were as follows: 1) MCL diagnosis; 2) Treatment with a first-line therapy; 3) Documented treatment response. The study's exclusion criteria included: 1) Patients not submitted to first-line therapy, either due to medical or patient's decision; 2)

Patients who started treatment recently and the response has not yet been evaluated. A total of 54 patients had a documented diagnosis of MCL. However, 7 patients were not treated due to medical or patient's decision and were not included in the final selection as well as 5 other patients whose treatment started too recently, and response was still not available. The final selection included a total of 42 patients.

2.3 Data collection and analysis

To study the factors that influenced treatment response, our patient's group was split according to age (<65 years and ≥65 years), presence of B symptoms, the patients' Charlson comorbidity index (≤6 and >6), involvement of digestive system, ECOG score (0-1 and 2-3), extranodal involvement, gender, MIPI (≤6.2 and >6.2), presence of medullar involvement, presence of splenomegaly and disease stage at diagnosis using the Ann Arbor staging system (I-III and IV). The complete response ratio to treatment of each subgroup was compared with the overall one, to observe whether there was any significant deviation from the mean. Lastly, we compared treatment responses within each group, using Aspin-Welch t-tests to account for the unknown and possibly unequal population standard deviations. That is, we analyzed if, for instance, patients with the presence of splenomegaly were more likely to respond to treatment compared with the absence of splenomegaly. We considered a factor to be determinant to the response to treatment (variable statistically significant) if, under the Aspin-Welch t-test, the difference in means between subgroups was statistically different from 0 to a 5% significant level.

3. Results

3.1 Patient characteristics

Of the 42 patients, 32 (76%) were male and 10 (24%) were female with an average age at diagnosis of 69 years. Regarding clinical presentation, 17 (40%) patients presented with B symptoms, 23 (45%) with splenomegaly, 25 patients (41%) had medullar involvement and 17 (40%) gastrointestinal involvement. At the time of diagnosis, 2 patients were staged as a stage II lymphoma, 9 as stage III and 31 as stage IV (approximately 74%). Twenty-six patients (62%) achieved complete response after their first-line therapy, 5 presented a partial response and 11 no response. Overall, 16 patients did not achieve complete response (38%). The first- line therapeutic choices were varied, with the most used regimens being R-CHOP (13) andR-CHOP/R-DHAP (11). Nine patients were submitted to an autologous stem cell transplant.

Table 1: Demographic and Baseline Clinical Characteristics

	(1)	(2)	(3)	(4)	(5)
Parameters	N	Mean	St. Dev.	Min	Max
Age of diagnosis	42	69	11.17	36	94
ECOG Performance Status	42	1	0.9606	0	3
Charlson Comorbidity Index	42	5.7	2.087	2	11
MIPI	42	6	0.70	5.3	8.3
Ann Arbor Stage	42	IV	0.5973	II	IV

Note: ECOG: Eastern Cooperative Oncology Group (ECOG) performance-status. MIPI: Simplified Mantle- Cell Lymphoma International Prognostic Index score. The index classifies patients as having low-, intermediate-, or high-risk disease, as defined by scores of 0 to 3, 4 or 5, and 6 to 11, respectively.

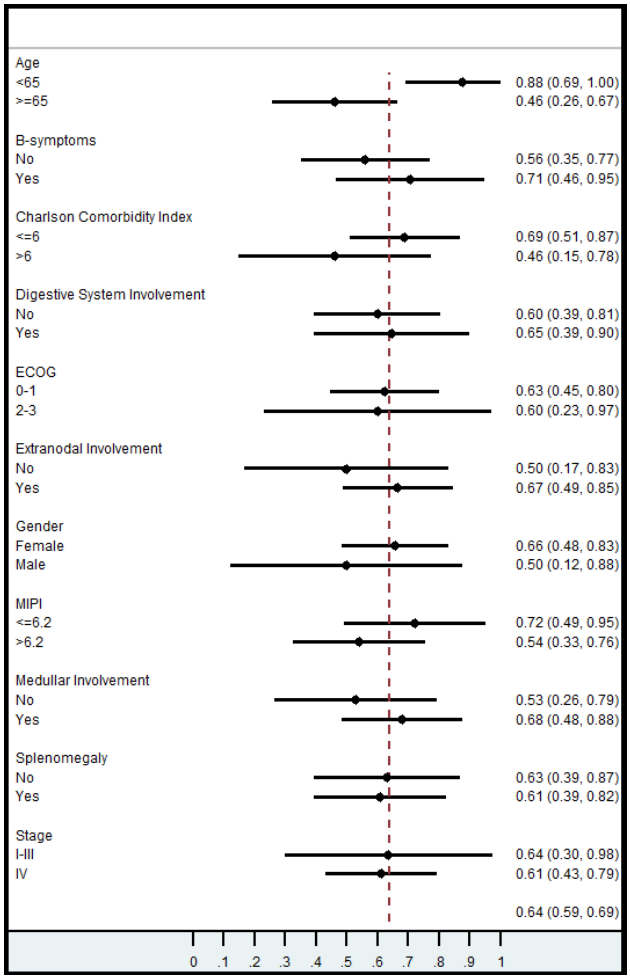

Figure 3: Association between studied clinical parameters and the outcome of first-line treatment

3.2 Outcomes

In order to assess if there was any characteristic, either biological or clinical, that made the response to treatment deviate significantly from the overall one, we analyzed the outcomes of first-line treatment for each subgroup of factors. Figure 3 displays the average response and respective 95% confidence interval of every subgroup. The dashed line shows the overall response of the population to first-line treatment, meaning that in the sample of 42 patients, 62% fully responded to treatment.

In almost all subgroups, treatment response did not differ much from the overall group. For

instance, the individuals with low Charlson Comorbidity Index, which we considered to be below or equal to 6, had an average complete response to treatment of 69% (confidence interval of 51% to 87%), while patients with higher index had an average response of 46% (confidence interval from 15% to 78%).

Regarding the patient's age at the time of diagnosis, the overall response rate for the younger patients (<65 years) was 88% (confidence interval from 69% to 100%) and for older patients was 46% (confidence interval from 26% to 67%).

The first analysis is helpful in determining if there are any characteristics that differ significantly from the total average. To further analyze differences in responses within group, Aspin-Welch's t-tests were conducted to compare if, for example, being younger or older than 65 years old had statistical influence on response to treatment. The results are displayed in Table 2.

It can be observed in Table 2 that the difference in responses rates between male and female patients is not statistically significant, as it yields a p-value of 0.417, way above the threshold of significance of 0.05. This seems to be the case for almost all variables, except age, whose significance is lower than the threshold.

Table 2: Comparison of treatment response by subgroup

	Group 0		Group 1		
Variable	Average Response	N_0	Average Response	N_1	p-value
Age	0.875	16	0.462	26	0.003
B-symptoms	0.56	25	0.706	17	0.345
Charlson CI	0.69	29	0.462	13	0.189
Dig. System Inv.	0.6	25	0.647	17	0.764
ECOG	0.625	32	0.6	10	0.894
Extranodal Inv.	0.5	12	0.667	30	0.35
Gender	0.656	32	0.5	10	0.417
MIPI	0.722	18	0.542	24	0.237
Medullar Inv.	0.529	17	0.68	25	0.344
Splenomegaly	0.631	19	0.609	23	0.883
Stage	0.636	11	0.613	31	0.896

Note: This table presents the average response to treatment divided by subgroup. Group 0 represents, by line: age <65y; absence of B-symptoms; Charlson Comorbidity Index ≤6; absence of involvement of digestive system; ECOG score 0-1; absence of extranodal involvement; female gender; MIPI ≤6.2; absence of medullar involvement; absence of splenomegaly; disease stage 0-3. Group 1 represents the opposite. The corresponding p-value regards the null hypothesis that the average responses between subgroups are equal.

4. Discussion

In this study, the average age at diagnosis was 69 years, with a predominance of male patients (76%) and the majority was staged as III or IV, which is in line with the most recent major review of the American Journal of Hematology. [24]

R-CHOP and R-DHAP were the most used regimens in first-line treatment of this sampleof patients (31% and 26% respectively), followed by an ASCT (21%) when indicated, which isin agreement with the ESMO clinical practice guidelines of 2017. [21]

Nevertheless, the effective treatment of patients with mantle cell lymphoma is still a challenge today, with up to half of the patients not achieving complete response without known influencing factors. [11, 21]. In this study, where complete response was achieved by 62% of patients, various factors were analyzed in their ability to influence treatment response. However, most of the factors could not predict the effectiveness of treatment. For example, patient's gender does not change the probability of an effective treatment (66% women achieving complete response rate comparing to 50% of men), as the difference in responses yields a p-value of 0.417.

Nonetheless, according to this study, we can observe that the overall response rate of the younger cohort deviates significantly from the overall mean (confidence interval between 69% and 100%). The average complete response rates for patients older or younger than 65 years of age were 47% and 88% respectively, with a p-value of 0.003. Furthermore, it should be noted that if, instead of a two-tailed Aspin-Welch t-test (which assesses if the difference in means is *different* from 0), we computed a one-tailed t-test, the p-value would change to 0.0015. This means that the difference in complete response rates between younger and older patients is significant; that is, we have statistical evidence that older patients have worse overall response rates than the younger group. This could explain why, in previous studies [12, 16], age above 65 years is considered a poor prognosis factor, which supports the use of age in the calculation

of the most widely accepted and validated MCL prognostic index, the MIPI.[11]

This study adds to the ongoing discussion about factors that could have a significant im-pact on the response to first-line therapy and could therefore alter the therapeutic decision thatare not considered in MIPI prognostic tool. Even though no factor other than age was statistically significant, patients with no B symptoms showed a tendency to a worse treatment response rate when compared to symptomatic patients (56% and 71% respectively). Consistentwith relevant studies that suggested a ”watch and wait” strategy in a selected group of patients,in particular, asymptomatic patients[15, 16], these findings support that the lower response to treatment of patients without B symptoms might not be enough to justify the risks of therapy.

Likewise, although not statistically significant, patients with a Charlson Comorbidity Index higher than 6 showed worse treatment response rates (46%) when compared to patients witha lower score (69%). Therefore, a higher Charlson Comorbidity Index could also be considereda predictor of worse treatment response. However, further studies are needed to confirm this hypothesis, hopefully introducing this index in MCL therapeutic decision.

The small sample size, which resulted in big standard deviations and limited statistical power, when compared to other studies, limits its conclusions, showing that larger studies are necessary. This study raises some important questions as to why some patients have better therapeutic results than others. If factors such as patient’s comorbidities or ECOG score do not seem to be relevant, probably the characteristics of the tumor may be more important than the performance status of the patient?

5. Conclusion

The aim of the study was to assess which factors influenced the response rate to first-line treatments. To meet this goal, patients who were diagnosed and treated for MCL in Centro Hospitalar e Universitario de Coimbra (CHUC) between February 2008 and November 2020 wereselected and 42 patients were included in the analysis.

We computed the complete response rate to treatment of each factor subgroup and compared with the overall one, to assess whether there was any subgroup whose response to treatment significantly differed from the one of the overall populations. Then we compared the responses to treatment within each group, using Aspin-Welch t-test to evaluate if a factor was determinant to the response to treatment. We considered a variable to be statistically significant if the corresponding p-value of the Aspin-Welch t-test was below 0.05 – meaning that thedifference in means between subgroups was statistically significant.

In conclusion, age is the only variable for which we have statistical support to infer that itimpacts the full response rate to treatment of MCL, with 87.5% of patients under 65 years old achieving complete response in contrast to only 46% patients above 65 years old.

References

[1] Larry H Argatoff, Joseph M Connors, Richard J Klasa, Douglas E Horsman, and Randy DGascoyne. Mantle cell lymphoma: a clinicopathologic study of 80 cases. *Blood, The Journal of the American Society of Hematology*, 89(6):2067–2078, 1997.

[2] Steven H Swerdlow, Elias Campo, Stefano A Pileri, Nancy Lee Harris, Harald Stein, Reiner Siebert, Ranjana Advani, Michele Ghielmini, Gilles A Salles, Andrew D Zelenetz,et al. The 2016 revision of the world health organization classification of lymphoid neoplasms. *Blood*, 127(20):2375–2390, 2016.

[3] Pedro Jares and Elias Campo. Advances in the understanding of mantle cell lymphoma. *British journal of haematology*, 142(2):149–165, 2008.

[4] Linda Kachuri, Laura E Beane Freeman, John J Spinelli, Aaron Blair, Manisha Pahwa, Stella Koutros, Shelia Hoar Zahm, Kenneth P Cantor, Dennis D Weisenburger, Punam Pahwa, et al. Insecticide use and risk of non-hodgkin lymphoma subtypes: A subset meta-analysis of the north american pooled project. *International Journal of Cancer*, 2020.

[5] Yu Wang and Shuangge Ma. Risk factors for etiology and prognosis of mantle cell lymphoma. *Expert review of hematology*, 7(2):233–243, 2014.

[6] Julie M Vose. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *American journal of hematology*, 92(8):806–813, 2017.

[7] Francesco Bertoni, Andrea Rinaldi, Emanuele Zucca, and Franco Cavalli. Update on the molecular biology of mantle cell lymphoma. *Hematological oncology*, 24(1):22–27, 2006.

[8] Roshni Narurkar, Mohammad Alkayem, and Delong Liu. Sox11 is a biomarker for cyclin d1-negative mantle cell lymphoma. *Biomarker research*, 4(1):1–3, 2016.

[9] Lina Nygren, Stefanie Baumgartner Wennerholm, Monika Klimkowska, Birger Christens-son, Eva Kimby, and Birgitta Sander. Prognostic role of sox11 in a population-based cohort of mantle cell lymphoma. *Blood, The Journal of the American Society of Hematology*, 119(18):4215–4223, 2012.

[10] Veròn ica Fernàndez, Olga Salamero, Blanca Espinet, Francesc Solé, Cristina Royo, Alba Navarro, Francisca Camacho, Sílvia Beà, Elena Hartmann, Virginia Amador, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. *Cancer research*, 70(4):1408–1418, 2010.

[11] Eva Hoster, Martin Dreyling, Wolfram Klapper, Christian Gisselbrecht, Achiel Van Hoof, Hanneke C Kluin-Nelemans, Michael Pfreundschuh, Marcel Reiser, Bernd Metzner, Hermann Einsele, et al. A new prognostic index (mipi) for patients with advanced-stage mantle cell lymphoma. *Blood*, 111(2):558–565, 2008.

[12] Simon Rule, Martin Dreyling, Andre Goy, Georg Hess, Rebecca Auer, Brad Kahl, Nora Cavazos, Black Liu, Shiyi Yang, Fong Clow, et al. Outcomes in 370 patients with mantlecell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *British journal of haematology*, 179(3):430–438, 2017.

[13] Eva Hoster, Wolfram Klapper, Olivier Hermine, Hanneke C Kluin-Nelemans, Jan Walewski, Achiel van Hoof, Marek Trneny, Christian H Geisler, Francesco Di Raimondo, Michal Szymczyk, et al. Confirmation of the mantle-cell lymphoma international prognostic index in randomized trials of the european mantle-cell lymphoma network. *Journalof Clinical Oncology*, 32(13):1338–1346, 2014.

[14] P Abrisqueta, DW Scott, GW Slack, C Steidl, A Mottok, RD Gascoyne, JM Connors, LH Sehn, KJ Savage, AS Gerrie, et al. Observation as the initial management strategy in

patients with mantle cell lymphoma. *Annals of Oncology*, 28(10):2489–2495, 2017.

[15] Jonathon B Cohen, Xuesong Han, Ahmedin Jemal, Elizabeth M Ward, and Christopher RFlowers. Deferred therapy is associated with improved overall survival in patients with newly diagnosed mantle cell lymphoma. *Cancer*, 122(15):2356–2363, 2016.

[16] Peter Martin, Amy Chadburn, Paul Christos, Karen Weil, Richard R Furman, Jia Ruan, Rebecca Elstrom, Ruben Niesvizky, Scott Ely, Maurizio DiLiberto, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol*, 27(8):1209–1213, 2009.

[17] Martin Dreyling, Georg Lenz, Eva Hoster, Achiel Van Hoof, Christian Gisselbrecht, Rudolf Schmits, Bernd Metzner, Lorenz Truemper, Marcel Reiser, Hjalmar Steinhauer, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survivalin mantle-cell lymphoma: results of a prospective randomized trial of the european mcl network. *Blood*, 105(7):2677–2684, 2005.

[18] J Vose, F Loberiza, P Bierman, G Bociek, and J Armitage. Mantle cell lymphoma (mcl): induction therapy with hypercvad/high-dose methotrexate and cytarabine (mc) (±rituximab) improves results of autologous stem cell transplant in first remission. *Journal of Clinical Oncology*, 24(18 suppl):7511–7511, 2006.

[19] Christian H Geisler, Arne Kolstad, Anna Laurell, Niels S Andersen, Lone B Pedersen, Mats Jerkeman, Mikael Eriksson, Marie Nordström, Eva Kimby, Anne Marie Boesen, et al. Long-term progression-free survival of mantle cell lymphoma after intensive frontline immunochemotherapy with in vivo–purged stem cell rescue: a nonrandomized phase 2 multicenter study by the nordic lymphoma group. *Blood, The Journal of the American Society of Hematology*, 112(7):2687–2693, 2008.

[20] BS Kahl, WL Longo, JC Eickhoff, J Zehnder, C Jones, J Blank, T McFarland, W Bottner, H Rezazedeh, J Werndli, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin oncology network. *Annals of oncology*, 17(9):1418–1423, 2006.

[21] M Dreyling, E Campo, O Hermine, M Jerkeman, S Le Gouill, Simon Rule, Ofer Shpilberg, J Walewski, and M Ladetto. Newly diagnosed and relapsed mantle cell lymphoma: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 28:iv62–iv71, 2017.

[22] Tadeusz Robak, Huiqiang Huang, Jie Jin, Jun Zhu, Ting Liu, Olga Samoilova, Halyna Pylypenko, Gregor Verhoef, Noppadol Siritanaratkul, Evgenii Osmanov, et al. Bortezomib-based therapy for newly diagnosed mantle cell lymphoma. *New England Journal of Medicine*, 372(10):944–953, 2015.

[23] Michael L Wang, Hun Lee, Hubert Chuang, Nicolaus Wagner-Bartak, Frederick Hagemeister, Jason Westin, Luis Fayad, Felipe Samaniego, Francesco Turturro, Yasuhiro Oki, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *The Lancet Oncology*, 17(1):48–56, 2016.

[24] Preetesh Jain and Michael Wang. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. *American journal of hematology*, 94(6):710–725,2019