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Clinical report

Mantle cell lymphoma, response to treatment and prognosis in 45 patients☆

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ABSTRACT

Background and purpose: Mantle cell lymphoma (MCL) is a rare lymphoproliferative disorder, with frequent relapses and a poor prognosis. This study analyzes response to treatment and prognosis in a series of MCL patients.
Patients and method: Retrospective study of MCL patients diagnosed in a single institution between 1996 and 2013. The cohort was divided according to the treatment received.
Results: Forty-five patients were included (32 male) with a median age of 66 years old. Twenty-one received intensive chemotherapy or chemoimmunotherapy (based on high-dose cytarabine), 13 semi-intensive (without high-dose cytarabine), 8 not intensive and 3 did not require treatment. Overall response rate was 85% in the intensive and 77% in the semi-intensive treatment groups. In multivariate analysis, intensive treatment was correlated with a longer progression-free survival (hazard ratio 9.8 [95% CI 2.7–35.5], $p = .001$) and overall survival (4.5 [1.2–17.8], $p = .03$).
Conclusions: In this retrospective series of MCL patients, intensive treatment was correlated with better outcomes than the other treatment modalities.

Linfoma de células del manto. Respuesta al tratamiento y pronóstico en 45 pacientes

Palabras clave:
Linfoma de células del manto
Dosis altas de citarabina
Pronóstico

RESUMEN

Fundamento y objetivo: El linfoma de células del manto (LCM) es un linfoma poco frecuente, con recaídas habituales y mal pronóstico. Este estudio analiza la respuesta al tratamiento y el pronóstico en una serie de pacientes con LCM.
Pacientes y método: Estudio retrospectivo de los pacientes con LCM diagnosticados en un centro entre 1996 y 2013. Se dividió la cohorte en función del tratamiento recibido.
Resultados: Se incluyeron 45 pacientes (32 varones) con una edad mediana de 66 años. Veintiún pacientes recibieron quimioterapia o quimioinmunoterapia intensiva (pautas con citarabina a dosis altas), 13 semi-intensiva (sin citarabina a dosis altas), 8 no intensiva y 3 no precisaron tratamiento. La respuesta global fue del 85% con tratamiento intensivo y del 77% con semiintensivo. En el análisis multivariable el tratamiento intensivo se asoció a una mayor probabilidad de supervivencia libre de progresión (SLP) y supervivencia global (SG) (*hazard ratio* de 9,8 [IC 95% 2,7-35,5], p = 0,001 para la SLP y 4,5 [1,2-17,8], p = 0,03 para la SG).
Conclusiones: En esta serie retrospectiva de pacientes con LCM el tratamiento intensivo se asoció a mejores resultados respecto al resto de las modalidades de tratamiento.

Introduction

Mantle cell lymphoma (MCL) is a non-Hodgkin's lymphoma characterised by translocation (11;14), which determines overexpression of cyclin D1, a regulatory protein of the cell cycle. It affects patients whose average age is 60, usually males, and constitutes

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7–9% of lymphomas in Europe.[1] It has different histological variants; some, like the blastoid, have a more aggressive evolution and worse prognosis. It usually presents itself in advanced stages with frequent extranodal involvement, especially in the digestive tube.[1] The Mantle Cell Lymphoma International Prognostic Index (MIPI),[2] which includes age, general condition (ECOG scale), serum lactate dehydrogenase and white blood cell count, categorises the MCL population into 3 prognostic groups. In a minority of cases, MCL has an indolent evolution and does not require treatment for months or years.[3] In most cases however, it has a poor prognosis, with a recurrent evolution but more aggressive than low-grade lymphoma malignancy. Current treatment consists of immunotherapy with rituximab[3–5] in combination with chemotherapy that includes, in young patients without comorbidity, regimens of high-dose cytarabine followed by consolidation with autologous hematopoietic stem cell transplantation (HSCT).[3,4,6,7] In elderly patients or those with comorbidities, immuno-chemotherapy guides such as R-CHOP or bendamustine-rituximab tend to be used followed by maintenance with rituximab,[3–5,8] while frail patients are usually administered monotherapy medications (usually alkylating).[3,4]

In this study we describe the characteristics of patients with MCL who have been treated in a facility and their response analysed in regard to the treatment provided.

Patients and methods

The medical records of patients with MCL treated in a centre between 1996 and 2013 were reviewed. To analyse the response to treatment, patients were categorised into 3 groups: intensive, semi-intensive and non-intensive. The guides followed in the intensive treatment group was HyperCVAD/MA (cyclophosphamide 300 mg/m^2/12 h days 1–3, vincristine 2 mg days 4 and 11, doxorubicin 50 mg/m^2 day 4, dexamethasone 40 mg/day days 1–4 and 11–14, methotrexate 1 g/m^2 day 15, cytarabine 3 g/m^2/12 h days 16 and 17) in combination or not with rituximab (375 mg/m^2, days 1 and 15 of the cycle). The semi-intensive treatment group received CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 day 1 and prednisone 100 mg days 1–5) or other guides similar to CHOP with or without rituximab (375 mg/m^2 day 1). The non-intensive treatment administered medications in monotherapy (chlorambucil or cyclophosphamide), with or without rituximab.

To study the response to treatment and survival, only patients who received intensive and semi-intensive treatment were considered. The response to treatment was assessed by computed tomography (CT) in all patients and with a biopsy of affected tissue at the time of diagnosis.[9] A complete response (CR) was considered the disappearance of the indicative malignant lesion by CT (and no evidence of the disease in a biopsy of the previously affected tissue) and a partial response, a decrease of more than 50% of measurable lesions (with or without persistence of the disease in the previously affected tissue) and the absence of new lesions. Overall survival (OS) was defined as the time from the diagnosis of the disease until death from any cause, and the progression-free survival (PFS) as the time from diagnosis until progression or death from any cause.[9]

A descriptive analysis of the sample was performed according to the study group. Comparisons between groups were performed using the chi-squared or Fisher *F* tests, as appropriate, in the case of qualitative variables, and using the Mann–Whitney *U* test for quantitative variables. The multivariate survival analysis was performed using the Cox proportional hazards model. A p-value of <0.05 was considered significant.

Results

There were 45 patients included in the study. Their demographic, clinical and biological data are shown in Table 1. The majority were men, with a good overall physical condition despite frequently showing an advanced stage and extranodal involvement (33/45, 73%), mainly bone marrow (32/45, 71%). Intensive treatment was administered to younger patients and with a lower MIPI (Table 1).

Treatment and response

Three patients (7%) had a disease with an indolent behaviour and did not require treatment. Of the remaining 42, 21 (50%) received intensive treatment, of which 10 consolidated response to HSCT and 11 did not (six due to mobilisation failure, four due to progression and one because of death during induction therapy); 13 (31%) received semi-intensive treatment (according to RCHOP guidelines) and eight (19%) received no intensive treatment.

There was no difference in the overall response rate between the intensive and semi-intensive groups (17 [85%] compared to

Table 1
Baseline characteristics according to treatment groups.

	General series (n = 45)	Intensive treatment (n = 21)[a]	Semi-intensive treatment (n = 13)[b]	Non-intensive treatment (n = 8)[c]	p[d]
Males, n (%)	32/45 (71)	14/21 (67)	10/13 (77)	5/8 (63)	0.704
Age (years), median (extremes)	66 (42–87)	60 (42–70)	69 (44–81)	82.5 (73–87)	**0.002**
Two or more extranodal sites, n (%)	10/45 (22)	6/21 (29)	3/13 (23)	1/8 (13)	1
Ann Arbour III–IV state, n (%)	41/45 (91)	19/21 (91)	11/13 (85)	8/8 (100)	0.627
ECOG ≥ 2, n (%)	7/43 (16)	1/20 (5)	4/12 (33)	2/8 (25)	0.053
MIPI, mean (SD)	6.2 (0.6)	6.1 (0.5)	6.6 (0.7)	6.5 (0.4)	**0.029**
Elevated LDH, n (%)	17/40 (43)	10/20 (50)	6/10 (60)	1/8 (13)	0.709
β_2 microglobulin > 2.4 mg/l, n (%)	19/36 (53)	8/19 (42)	5/8 (63)	6/7 (86)	0.420
Haemoglobin (g/l), median (extremes)	112 (66–158)	119.5 (66–151)	105.5 (96–152)	110 (101–133)	0.660
Leucocytes ($\times 10^9$/l), median (extremes)	7 (2.4–224)	8 (4–107.3)	5.7 (2.4–96)	5.8 (4–224)	0.129
Platelets ($\times 10^9$/l), median (extremes)	162 (25–374)	157.5 (25–374)	148 (65–258)	166 (104–337)	0.628
Lymphocytes ($\times 10^9$/l), median (extremes)	2.9 (0.4–109)	3.4 (0.5–44)	2.3 (0.4–86)	1.7 (0.8–109)	0.226

SD: standard deviation; ECOG Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MIPI: *Mantle Cell Lymphoma International Prognostic Index.*

[a] Eighteen patients with RHyperCVAD/MA, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine, two with HyperCVAD/MA, one with BURKIMAB (immunochemotherapy based with high-dose methotrexate and cytarabine).

[b] Five patients with R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisone), four with RCOP (rituximab, cyclophosphamide, vincristine and prednisone), two with R-CHVelcP (rituximab, cyclophosphamide, adriamycin, bortezomib and prednisone), one with CHOP (cyclophosphamide, adriamycin, vincristine and prednisone), and another with CNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, and prednisone).

[c] Six patients with chlorambucil-prednisone, one with rituximab-cyclophosphamide and another one with chlorambucil-vincristine.

[d] Resulting from the comparison between the intensive and semi-intensive therapy groups.

Bold indicates statistical significance.