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Review

Mantle cell lymphoma: Towards a personalized therapeutic strategy?☆

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ABSTRACT

Mantle cell lymphoma (MCL) is a clinically heterogeneous non-Hodgkin lymphoma with an aggressive clinical behaviour and short survival in some cases and an indolent course in others. Advances in the biology and pathogenesis of MCL have unveiled several genes involved in deregulation of cell cycle checkpoints and the finding of subclonal populations with specific recurrent mutations (*p53*, *ATM*, *NOTCH2*) with an impact on disease progression and refractoriness to treatment. Prognostic stratification helps to distinguish between indolent and aggressive forms of MCL. Currently, younger fit patients benefit from more intensive front line chemotherapy regimens and consolidation with autologous transplantation, while older or frail patients are treated with less intensive regimens and rituximab maintenance. For relapsing disease, the introduction of bortezomib and lenalidomide containing regimens and B-cell receptor pathway inhibitors such as ibrutinib and idelalisib in combination with immunochemotherapy have emerged as therapeutic agents with promising clinical outcomes.

Linfoma de células del manto: ¿hacia una estrategia terapéutica individualizada?

Palabras clave:
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RESUMEN

El linfoma de células del manto (LM) es una entidad clínica heterogénea con un comportamiento clínico agresivo y una supervivencia corta en algunos pacientes, mientras que en otros sigue un curso clínico indolente. Los recientes avances en la biología del LM han demostrado la existencia de genes implicados en la desregulación de vías relacionadas con el ciclo celular, así como la presencia de poblaciones subclonales con mutaciones recurrentes *(p53*, *ATM*, *NOTCH2)* con impacto en la progresión clínica y refractariedad al tratamiento. La estratificación pronóstica ayuda a distinguir entre formas indolentes y agresivas del LM. Actualmente, los pacientes jóvenes se benefician de quimioterapia alternante y consolidación con trasplante autólogo en primera línea, y los pacientes ancianos se tratan con regímenes estándar y mantenimiento con rituximab. Los pacientes en recaída se benefician de regímenes que incluyen bortezomib y lenalidomida. Además, el empleo de inhibidores de tirosincinasas (ibrutinib, idelalisib) está ofreciendo resultados clínicos muy prometedores.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a haematological neoplasia which is incurable with conventional immuno-chemical regimes. It represents 4–9% of non-Hodgkin lymphomas (NHL). MCL is a B-cell NHL which generally affects males (2.5:1) over 60, and usually presents in advanced clinical stages, with medullar involvement (70%), expression in the peripheral blood system (35%), generalised adenopathies and splenomegaly. Extranodal involvement is also common in the gastrointestinal tract (stomach, colon) (80%),

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Table 1
Differential diagnosis of mantle cell lymphoma with other chronic B-cell lymphopfoliferative disease according to immunophenotypic and genetic alterations.

Entity	IgS	CD5	CD10	CD11c	CD19	CD20	CD22	CD23	FMC7	CD25	SOX11	Genertic disorders
MCL	+	++	–	–	+	+	+	–/+	+	–	+	8p–,t(11;14)(*bcl-1*),11q–,*p53*
CLL	+/–	++	–	–/+	+	+/–	–/+	++	–/+	–/+	–	6q–,11q–,+12,13q–,17p– (*p53*)
PL	++	+	–	–/+	+	+/–	+	+/–	++	–	–	6q–,t(11;14),14q+,mut*p53*
FL	+	–	+	–	+	++	+	–/+	++	–	–	t(14;18)(q32;q21)(*bcl-2*)
LPL	+/–	–/+	–	–	+	+/–	+/–	–/+	+	+/–	–	t(9;14)(p13;q32)(*PAX5*)
SMZL	+	–/+	–/+	+	+	+	+/–	–/+	+	–	–	+3,3q+,7q–
DLBCL	++	–/+	–	–	+	++	+	–	+	–	––	3q27+,8q24+,t(14;18)

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL: chronic lymphocytic leukaemia; LPL: lymphoplasmacytic lymphoma; MCL: mantle cell lymphoma; SMZL: splenic marginal zone lymphoma; PL: prolymphocytic leukaemia; mut*p53*: *p53 mutations*; *p53:* deletion of the *p53* gene in 17p13.1; + the majority of cases express the surface antigen; ++: intense expression in the majority of cases; – the majority of cases are negative; +/–: weak/moderate expression in the majority of cases; –/+: the majority of cases do not express the antigen or express it with a variable intensity.

the liver and the Waldeyer ring. Other extranodal involvements include the skin, tear-producing glands and the central nervous system.[1,2] MCL was originally classified as a lymphocytic lymphoma of intermediate differentiation. The WHO classification later described MCL as a lymphoma with characteristics which were different from the other B-cell NHL and with aggressive clinical behaviour patterns.[3] The cellular origin of the MCL lymphocytes is the peripheral area of the germinal centre or the follicular mantle. There are 4 morphological variants: nodular or classical, marginal area variant, pleomorphic and blastic. The classical variant consists of lymphocytes fairly small in size, a polymorphic nucleus with chromatin content, which is jagged in form and with one or 2 shallow indentations. The nucleoli are small or negligible in size, and there is little cytoplasm. The blastic variant is characterised by the presence of larger, pleomorphic lymphocytes, a centrocytoid nucleus with visible nucleoli, great mitotic activity and an aggressive clinical course.[4]

Diagnosis and pathogenic mechanisms

MCL diagnosis is established through histological testing (node or bone marrow biopsy), immunophenotypic and molecular testing in the majority of cases. The lymph node usually presents as a nodular infiltration pattern, although it generally progresses to a diffuse pattern. Bone biopsy shows a nodular, interstitial or paratrabecular infiltration pattern, although it usually evolves into a diffuse pattern. MCL cells intensely express surface immunoglobulins, panB markers (CD19, CD20, CD22), FMC-7, CD79b and also test positive for CD5 and negative for CD10 and CD23 in lymph nodes, with weak positive references in blood and bone marrow. Differential diagnosis should be established with chronic B lymphocytic leukaemia (LLC-B) (both entities express CD5, but MCL usually tests negative for CD23), the downy splenic lymphoma in nodular form, prolymphocytic B leukaemia and diffuse large cell lymphoma in its blastic form (Table 1). A common genetic disorder of this disease is t translocation (11; 14)(q13;q32), observed in 40–70% of cases with conventional cytogenetic tests and in over 95% with in situ fluorescent hybridisation. In molecular terms, it is characterised by the presentation of an increase in the D1 cyclin expression as a consequence of t(11;14) and deregulation of the *bcl-1* gene (11q13) due to its juxtaposition with the heavy chain gene of immunoglobulins (IgH) in 14q32. This genetic disorder is considered as a primary oncogenic mechanism in MCL progression. However, MCL cases have also been described with standard morphology which does not express cyclin D1, but are positive for cyclin D2 and which present a more aggressive clinical behaviour that is refractory to medical treatment.[5,6] Other genetic modifications include chromosome deletions 11q22-q23 (where *ATM* and *BITR3* genes reside) and 13q14 (includes the *RB1* gene) at a similar percentage to that observed in CLL-B and much more frequent than in other chronic lymphoproliferative syndromes (cLPS). Furthermore, mutations of the *ATM* gene together with the deletion of the other allele in 11q22-q23 have been detected in approximately 70% of cases and are associated with chromosome instability. The deletions of chromosome 17p13.1 (where gene *p53* resides) and the mutations of the other *TP53* allele are generally observed in blastic cell forms and are associated with refractive treatment outcome and a short term survival outcome.[7] The expression of SOX11 has recently been described as a diagnostic biomarker of MCL which is expressed in practically the majority of cases and which is, in contrast, negative in other mature SLPc and in normal B cell lymphocytes in any differentiation stage.[8] A molecular pathogenic model has therefore been described regarding the expression of SOX11 which includes 2 molecular subtypes of MCL. One subtype emerges from the lymphatic follicle mantle, causes an in situ MCL lesion and is a carrier of translocation t(11;14). These cells express SOX11, are genetically unstable and present frequent mutations in genes related to cellular cycle pathway regulation (*INK4a/CDK4/RB1, ARF/MDM2/p53*). In contrast, lymphocytes with t(11;14) with access to the germinal centre present with somatic hypermutations of the *IGHV* genes, are negative for SOX11, genetically more stable and are associated with types of disease with splenic involvement, expression in blood and low nodal involvement.[9]

Recent studies based on massive sequencing techniques of the genome/exome in 29 cases of MCL have identified 25 genes with recurrent clonal or subclonal mutations which have an impact on the clinical aggression of this disease, either facilitating clinical progression to diagnosis, or in the potential selection of subclones which lead to treatment resistance. In particular, the presence of mutations in *NOTCH2* have been described; these are associated with aggressive forms of the disease and adverse prognosis.[10]

Clinical presentation and prognostic staging

MCL is a clinically heterogeneous disease. Half of patients present with constitutional symptoms when diagnosed, whilst the other half are asymptomatic. Clinically, non voluminous (2–5 cm) general peripheral adenomegalies and splenomegaly are present. Some patients may present again with a more aggressive clinical condition, with voluminous adenomegalies and blastic morphology. 20–25% of patients with nodular morphology may develop blastic forms and these are associated with being treatment refractory and with short term survival. Mean MCL survival varies from 3 to 7 years in patients treated with standard chemotherapy.[11] This broad survival variation is the result of several patients presenting with an indolent course of the disease accompanied by prolonged survival, whilst other patients who present with blastic forms of the disease on diagnosis, undergo a more aggressive disease course with a short survival outcome.

It has also been observed that prognosis for leukemised MCL is lower than for lymphoma with no peripheral expression.