Mantle cell lymphoma: from pathology and molecular pathogenesis to new therapeutic perspectives

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Mantle cell lymphoma (MCL) is a well defined lymphoid neoplasm genetically characterized by the t(11;14)(q13;q32) translocation leading to a constitutive overexpression of cyclin D1.[1,2] This lymphoma is composed of a monomorphic proliferation of small to medium sized lymphoid cells with irregular nuclei of mature B-cell phenotype commonly co-expressing CD5. The correlations between these specific pathological characteristics and the genetic and molecular alterations have been crucial in defining this lymphoma and recognizing its broad morphological and clinical manifestations, which in turn have lead to a better understanding of the molecular mechanisms underlying the development and progression of the disease. The clinical behavior is very aggressive and few patients reach long survival with current therapeutic protocols and even fewer may be considered cured. The better knowledge of this disease, the development of new preclinical models, and the emergence of a new generation of drugs are facilitating the design of new therapeutic strategies that may overcome the resistance of this aggressive lymphoma to conventional treatments and may improve the life expectancy of the patients.

Clinical manifestations

MCL accounts for about 3 to 10% of all non-Hodgkin's lymphoma with a predominance in elderly males. Most patients present in stage IV disease with generalized lymphadenopathy, hepatosplenomegaly, and bone marrow involvement, but bulky disease and B symptoms are less common. Extranodal involvement is relatively frequent but an extranodal presentation without apparent lymphadenopathy only occurs in 4-15% of the cases. Central nervous system (CNS) involvement may occur in 10-20% of the patients but, in contrast to other extranodal sites, usually appears as a late event in the evolution of the disease.[1] Peripheral blood expression is almost constant in this disease, although in same cases it is only detected by flow cytometry analysis. The clinical evolution in most patients is relatively aggressive with poor response to conventional therapeutic regimens. The median overall survival is 3 to 4 years.[1,2] However, some patients with a predominantly leukemic form of MCL and no or minimal lymphadenopathy but common splenomegaly have a more indolent clinical course with a median survival of 6 years (range 2-11 years).[3] Interestingly, some of these patients may be asymptomatic and with no need therapy for more than 5 years.[3-5] The current treatments obtain complete remissions in 35% of cases, but the disease-free survival period is short and very few patients reach long-term remissions. After relapse, patients may have a relatively slow course for several months with enlargement of lymph nodes and increased resistance to chemotherapy that is followed by a more rapid and progressive evolution in a final accelerated phase. Patients with blastoid MCL have a poor response to therapy and usually fail to obtain a complete remission; this is associated with a rapid clinical course and death from progressive disease. In patients who do achieve a complete remission, the duration of the response is usually short and virtually all patients relapse in less than one year.[1,2]

Morphological and phenotypic characteristics

There is a broad spectrum of architectural and cytological features in MCL. Nodal involvement usually adopts mantle zone, nodular or diffuse growth patterns that may be related in part to the underlying meshwork of follicular dendritic cells. Two main cytological vari-

ants have been recognized. The *typical* or *classical* subtype is characterized by a monotonous proliferation of small to medium sized lymphocytes with scant cytoplasm, variably irregular nuclei and inconspicuous nucleoli. Some cases may have round nuclei resembling those seen in chronic lymphocytic leukemia (CLL) but in these cases prolymphocytes or paraimmunoblasts are not usually seen. The *blastoid* variant is clinically more aggressive and includes tumors with blastic morphology resembling lymphoblasts and cases with larger and pleomorphic cells mimicking large cell lymphomas.[1,2] These morphological variants should be considered as ends of a spectrum and some tumors may show overlapping morphological features between the variants.[6] In some cases the tumor cells may have large clear cytoplasm resembling monocytoid cells that can be morphologically difficult to distinguish from marginal zone lymphomas.[7] The tumor cells express a mature B-cell phenotype with surface IgM and IgD, frequent λ light chain and co-expression of the T-cell-associated antigen CD5 in virtually all cases. CD43 is also frequently expressed but CD23 and the follicular center markers CD10 and bcl-6 are usually negative. Phenotypic variants may include negativity for CD5, and occasional expression of CD10, bcl-6 or the T-cell markers CD8 or CD7.[1,2]

Pathogenetic mechanisms: deregulation of cell cycle and DNA damage response pathways

The genetic hallmark of MCL is the 11q14 translocation leading to overexpression of cyclin D1, which may facilitate the malignant transformation of the lymphoid cell by deregulating the cell cycle control of these cells. Interestingly, a recent microarray study of MCL identified a small subset of cyclin D1-negative tumors that had a similar expression profile, morphology, and phenotype as had cyclin D1-positive cases. These tumors did not carry the t(11;14) translocation but overexpressed either cyclin D2 or D3 emphasizing the relevance of the deregulation of the G1 phase of the cell cycle in the pathogenesis of these tumors.[8] Analyses of the JH/bcl-1 breakpoints have suggested that this translocation is predominantly generated during a primary DH-JH rearrangement in early B cells.[9] The identification of no or very few somatic mutations in immunoglobulin genes in most cases of MCL has confirmed that this lymphoma originates from pregerminal center cells.[10] However, 20-35% of cases of MCL do carry somatic hypermutations in the immunoglobulin genes and a biased use of the VH[4-34] and VH[3-21] genes in the rearrangements, suggesting that these tumors may originate from specific subsets of B cells that have entered the follicular germinal center.[3,11] However, unlike the situation in chronic lymphocytic leukemia, the hypermutational status of the immunoglobulin genes in MCL is not of prognostic significance and is not associated with ZAP-70 expression.[11,12]

In addition to the t(11;14) translocation, MCL variants with high proliferative activity and clinically aggressive behavior have frequent aberrations in other elements of the two major regulatory pathways of the cell cycle and senescence which include

Table 1. Number of chromosomal imbalances detected by comparative genomic hybridization in non-Hodgkin's lymphoma.

Diagnosis	% altered cases	Median number of alterations/case
Mantle cell lymphoma[17,46-49]	89	4.2
Blastoid-MCL[1]	100	10.1
Chronic lymphoma leukemia[50-53]	63	2.5
Progressed-CLL[53]	89	4.7
Follicular lymphoma[54-57]	68	2.2
Marginal zone lymphoma[58,59]	81	2.3
Large B-cell lymphoma[60-65]	75	3.4
Primary mediastinal B-cell lymphoma[65-67]	88	4
Multiple myeloma[68,69]	83	5.8

ARF/MDM2/p53 and *p16INK4A/CDK4* genes, respectively.[13] Thus, some aggressive tumors have simultaneous inactivation of both pathways by homozygous deletions of the whole *INK4/ARF* locus encoding for the p53 regulatory gene *ARF* and the CDK4 inhibitor *p16INK4A*. Alternatively, other tumors show concomitant inactivating mutations of p53 and amplifications of the *CDK4* gene.[14] Finally, other tumors have amplifications of the *BMI1* gene, an upstream inhibitor of both *ARF* and *p16INK4A*.

The importance of proliferation as one of the best indicators of the clinical behavior of MCL was clearly identified in early clinico-pathologic studies of these tumors. A recent microarray study has confirmed these findings and has suggested that the quantification of the proliferation gene signature may represent an integrator measurement of different oncogenic events targeting cell cycle in MCL.[15] Interestingly, the lymphomas developed in a recent cyclin D1 transgenic animal model generated by a cyclin D1 mutant refractory to nuclear export also carried secondary oncogenic events in the *ARF/MDM2/p53* pathway[16] indicating the importance of co-operative oncogenic events in the progression of cyclin D1-driven tumors.

Cytogenetic studies have demonstrated that MCL is one of the lymphoid neoplasms with the highest number of chromosomal aberrations that may target other genes involved in the progression of the tumors (Table 1).[17] The high number of genetic alterations in MCL compared to other lymphomas and the presence of frequent tetraploid clones suggests that alterations in the mechanisms regulating genomic stability and cell cycle checkpoints may also have an important role in the pathogenesis of these tumors.[13] In this sense, *ATM*, a gene located in the chromosomal region 11q22-23 frequently deleted in MCL, plays a central role in the cellular response to DNA damage. This gene is deleted and mutated in 40-75% of MCL, particularly in cases with a high number of chromosomal alterations.[18] CHK2 and CHK1 are two kinases that act downstream of ATM and prevent cell cycle progression in response to DNA damage signals. Decreased protein levels of these kinases and mutations of CHK2 have been described in a subset of MCL with a high number of chromosomal imbalances.[13] Mutations of ATM and CHK2 have been detected in the germline of some

Table 2. Lymphoma cell lines carrying the t(11;14)(q13;q32) translocation.

	HBL-2[70]	JVM-2[71]	SP-49/-50B/-53[72]	REC-1[73]	NCEB-1[30]	GRANTA-519[74,75]	Mino[76]	Z-138[77]	JEKO-1[78]	M-1[79]	UPN-1[33]	UPN-2[33]	MAVER-1 (Zamo et al.)
Age/Gender	84/M	63/F	58/F	61/F	57/M	58/F	64/F	70/M	78/M	58/M	52/M	57/M	77/M
Original diagnosis	DLCL	PLL	ILL	MCL	DCb/CcL	MCL	MCL	Blastoid MCL	MCL	Blastoid MCL	Blastoid MCL	MCL	MCL
Sample	LN	PB	PB	LN	PB	PB	PB	BM	PB	PB	Pleural effusion	Pleural effusion	PB
Cyclin D1 overexpression	++	+	+	++	+	+	+	++	+	++	++	+	
CD5	–	+	–		+	–	+	–	+	+	+	+	+
CD23	+	+	+		+	+	–	–	–	–	–	+	–
EBV	–	+	–/+/–	–	+	+	–	–	–	+	–	–	–
Ploidy	2N	2N	3N	2N-	4N-	2N-	3N+	2N+	3N-	2N+	2N-	3N+	2N
CC/M-FISH/SKY	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
mCGH/aCGH	yes	yes	yes	yes	yes	yes		yes	yes		yes	yes	
p53 status	del/*	wt/wt		wt/wt	del/mut	del/wt	#/mut	wt/*	del/mut		#/mut	del/mut	del/mut
ATM status		wt/wt		wt/*	del/*¶	del/mut¶			ampl/*		#/polymorph	#/mut	del/*
p16INK4A status	del/*	wt/#		Hom del	wt	Hom del		del/*	del/*				del/*
p16ink4a exp WB	–	+	–		+	–	+	–	+				-
Other oncogenes						BCL-2 amp					C-MYC R BCL-2 amp	C-MYC R	C-MYC R

*M: male; F: female; DLCL: diffuse large cell lymphoma; DCbCcL: diffuse centroblastic centrocytic lymphoma; ILL: intermediate lymphocytic lymphoma; PLL: prolymphocytic leukemia; LN, lymph node; PB, peripheral blood; EBV: Epstein-Barr virus; CC: conventional cytogenetics; M-FISH: multicolor fluorescence in situ hybridization; SKY: multicolor spectral karyotyping; mCGH: metaphase comparative genomic hybridization; aCGH, array comparative genomic hybridization; Del: heterozygous deletion; mut: mutated; homo del: homozygous deletion; wt:wild type; ¶ATM protein expression negative; WB: western blot, +: positive expression; ++: strong expression; –: negative/no detectable expression; *mutational analysis not performed; #deletions not analyzed.*

MCL patients suggesting that dysfunction of these genes may be an early phenomenon in the development of MCL and may have a predisposing effect. However, no alterations of these genes have been detected in familial aggregations of MCL or other lymphoid neoplasms.[19]

Models for preclinical studies: MCL cell lines and animal models

Experimental models of MCL are important tools for investigating the mechanisms involved in the pathogenesis of these tumors. These models are becoming essential to assess the plethora of new drugs that have been designed in the last yeas in attempts to target the aberrant molecular mechanisms involved in the development and progression of tumors. Preclinical studies are usually performed in cell lines and animal models that are presumably closely related to the human tumor. Although the current models have important limitations,[20] they do provide information that may be useful for designing clinical trials selecting drugs, patients, and strategies that could improve the outcome of the patients. Cell lines provide an unlimited supply of a relatively uniform cell population. Given the heterogeneity of human tumors, and particularly of MCL, it is important to have a large number of cell lines that mimic the variability of the clinical situations. In the last years several cell lines have been derived from MCL. Some other cell lines, obtained before this entity was well defined, have been reinterpreted as having originated in these tumors (Table 2). Contrariwise, the cell lines HF-4a and HF-4b, although generated supposedly from a MCL, carry the t(14;18)(q32;q21) transloca-tion and most probably correspond to follicular lymphomas.[21] The characterization of these cell lines is irregular but provides a broad spectrum of the phenotypic, genetic and molecular characteristics of MCL.

In this issue of the journal, Zamo et al. describe a new, very well characterized MCL cell line carrying p53 mutations, ATM deletion and a 8q24 (C-MYC) rearrangement. The phenotype of these cell lines is variable. In contrast to the relatively constant CD5 expression and CD23 negativity in human tumors, some cell lines are CD5-negative and CD23-positive. Interestingly, Zamo et al. demonstrate in their study that CD5 expression may be modulated with time. All the cell lines included in Table 2 have the t(11;14)(q13;q32) translocation although in some of them it was cryptic and only detected by fluorescence in situ hybridization (FISH) or multicolor-FISH studies. Cyclin D1 is expressed in all the lines examined although at different levels. Interestingly, JVM2, derived from a prolymphocytic leukemia, now considered as a morphological variant of MCL, also expressed cyclin D2. Several MCL cell lines are infected by the Epstein-Barr virus (EBV)(Table 2). The presence of the virus in cell lines is a marked difference from primary tumors and may have some influence on the biology of the cells. Thus, in isogenic cell lines derived from the same tumor the EBV-positive clone showed stronger tumorigenic properties than did the negative clone.[22] MCL primary tumors and cell lines have activation of the NF-κB pathways.[23] The activation of NF-κB pathways in EBV-infected lymphoid cells may complicate the interpretation of experimental studies using EBV-positive MCL cell lines.[24]
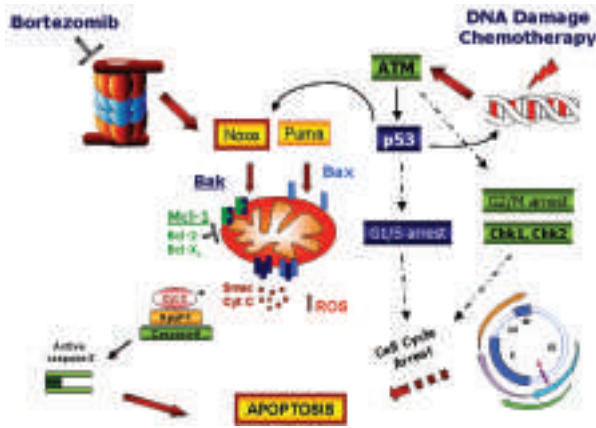
Figure 1. Apoptosis induction by chemotherapeutic agents. DNA damaging agents activate the ATM/p53 pathway which leads either to cell cycle arrest, DNA repair or apoptosis, according to the level of injury. In this last situation, p53 induces the pro-apoptotic *BH-3 only proteins*, Puma and Noxa, which are able to displace pro-apoptotic Bak from anti-apoptotic Mcl-1 sequestration. Once released, Bak can homodimerize or heterodimerize with Bax at the outer mitochondrial membrane, leading to mitochondrial depolarization. Concomitantly, cytocrome C and *Smac/Diablo* are released to the cytosol where they initiate caspase activation and cell death. The proteasome inhibitor bortezomib induces apoptosis in a p53-independent manner by activating Noxa transcription and therefore promoting the apoptotic mitochondrial pathway.

Conventional and molecular genetic studies including multicolor-FISH, spectral karyotyping (SKY) and array comparative genomic hybridization (CGH) have been performed in most MCL cell lines.[25-28] The genetic alterations observed in these cell lines reproduce the complex karyotypes of the primary tumors and several cell lines may represent different models of chromosomal instability.[28] Curiously, we have recently observed that NCEB-1 carries five to eight stable murine chromosomes and expresses both human and murine bcl-2 protein.[28] This phenomenon is different from that occurring in the most common inter- and intra-species cross-contamination among cell lines[29] since the murine chromosomes were integrated in the human cell lines. How this cell line acquired the murine chromosomes is not clear but it may have occurred during the early passages of the cell derivation since the cells were co-cultured with mouse peritoneal macrophages[30] The functional significance of this finding is not known but it is curious that this cell line has been relatively resistant to different drug treatments in *in vitro* experiments.[31] Several studies have characterized the molecular alterations of most of the cell lines. Similarly to the findings in human tumors, most of the cell lines showed an alternative inactivation of the *p53* and *p16INK4A* genes. Only MAVER-1 seems to have a concomitant mutation of *p53* and lack of expression of *p16INK4A* associated with deletion of the gene. *ATM* and p53 do not seem to be alternative mechanisms since inactivation of both genes are present in NCEB-1 and UPN-2 although *ATM* and *p53* mutations occur independently in other MCL cell lines. In addition to cell lines, some

authors have used animal models to study MCL experimentally. Unfortunately, transgenic animals overexpressing cyclin D1 generate lymphomas that are not similar to human MCL.[16,32] An alternative model is the use MCL cell lines as xenografts in immunodeficient mice. These grafts seems to retain the properties of the human tumors with disseminated and leukemic disease that may be used for experimental studies of new drugs and treatments.[33]

New therapeutic approaches to MCL

Although several standard therapeutic approaches have improved the outcome of MCL patients, this disease remains incurable.[34] In the last years new therapies targeting crucial biological cellular pathways have been proposed. Recently, the results of two separate phase II clinical trials conducted in patients with relapsed or refractory MCL treated with bortezomib (PS-341, Velcade®), a proteasome inhibitor, have been reported. Both trials have shown promising results, with an overall response rate greater than 40% and a relatively long duration of the responses using bortezomib as a single agent in intensively treated patients.[35,36] Protein degradation by the proteasome system is crucial for controlling the availability of regulatory proteins in the cell. Thus, several of these pathways regulated by proteasomes such as cyclin D1, p53 and NF-κB are not functional in many MCL cells, justifying the emergence of the proteasome as an attractive target for MCL treatment. We recently demonstrated in *in vitro* studies that bortezomib exerts its cytotoxicity in MCL cells through the generation of reactive oxygen species and the induction of the pro-apoptotic, BH-3 only protein Noxa. Thus, although proteasome inhibition induced the accumulation of the anti-apoptotic protein Mcl-1, due to the inhibition of proteasome degradation, activation of Noxa might antagonize the unwanted accumulation of Mcl-1 and also promote Bak release and therefore the induction of apoptosis[37] (Figure 1).

Mammalian target of rapamycin (mTOR) inhibitors have also emerged as promising agents for cancer therapy.[34] The mTOR pathway is a central controller of cell growth and proliferation in mammalian cells. Thus, mTOR kinase activity enhances mRNA translation of cell cycle encoding proteins, including cyclin D1. A phase II clinical trial using the synthetic mTOR inhibitor temsirolimus/CCI-779, a rapamycin analog, has shown that this inihibitor has antitumor activity in relapsed MCL, with an overall response rate of 38% and a median time-to-progression of 6.5 months.[34] *In vitro* assays in MCL cell lines have also demonstrated that the natural mTOR inhibitor rapamycin induces cell cycle arrest without induction of apoptosis.[38] These results suggest the potential use of this cytostatic agent in combination with other cytotoxic drugs. Flavopiridol, an inhibitor of cyclin D kinases (CDK), has also been used. A phase II trial in relapsed MCL patients showed a modest activity of flavopiridol as a single agent.[39,40] CYC202 (Seliciclib, R-roscovitine), another CDK inhibitor specific for CDK2-cyclin E, CDK7-cyclin H and CDK9-cyclin complexes, has also been tested in MCL cell lines. This com-

pound induces apoptosis in MCL cell lines by causing G$_2$-M cell cycle arrest and downregulation of cyclin D1 and Mcl-1 proteins, possibly associated with the observed dowregulation of RNA polymerase II and the transcription factor E2F-1.[41]

Thalidomide, an immunomodulatory drug with a plethora of cellular effects such as modulation of cytokine secretion, expression of adhesion molecules, activation of T, NK and denditric cells, angiogenesis and NF-κB inhibition,[34] has shown potential antitumor effect with a low toxicity profile in relapsed MCL, both alone[42] and in combination with rituximab[43] in a limited number of patients. Studies of rituximab plus CHOP plus thalidomide as induction treatment, followed by thalidomide maintenance are currently being evaluated. Some other drugs that have been tested *in vitro* using primary cells from MCL patients and cell lines are retinoic acid[44] and histone deacetylase (HDAC) inhibitors[45] alone or in combination with standard chemotherapy. All this research may help to understand the apoptotic pathways in MCL better and to identify new therapeutic agents.

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