Mantle Cell Lymphoma

1. Introduction: Mantle cell lymphoma (MCL) is a rare and aggressive form of non-Hodgkin's lymphoma defined by cyclin D1 overexpression or t(11;14) chromosomal translocation that generally affects older individuals and continues to have one of the worst outcomes of all the lymphomas *(Elias Campo et, al Blood 2015*). Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin lymphoma with distinctive clinical, biologic, and molecular characteristics. MCL comprises 4% to 8% of total non-Hodgkin lymphomas. The median age at diagnosis is 68, with male predominance (3:1). The disease often initially responds to treatment, but disease relapse inevitably occurs as with disseminated indolent lymphomas. However, the clinical behaviour of MCL usually is aggressive *(Cheah et al, JCO 2016)*

MCL diagnosis is made on a biopsy of a lymph node, tissue, bone marrow or blood phenotype which shows the typical morphology of monomorphic small to medium sized lymphoid cells with irregular nuclear contours *(Mckay et al, BJH 2012)*

- Four cytologic variants of MCL are recognized- small cell variant, mantle zone variant; diffuse variant, and the blastic variant
- Blastic variant is clinically more relevant because of its aggressive course of disease

2. Epidemiology: Mantle Cell Lymphoma represents 4% to 8% of non-Hodgkin's lymphomas. It primarily affects older individuals; males more than females by a ratio of about 4 to 1. The median age at diagnosis is approximately 58 years of age.

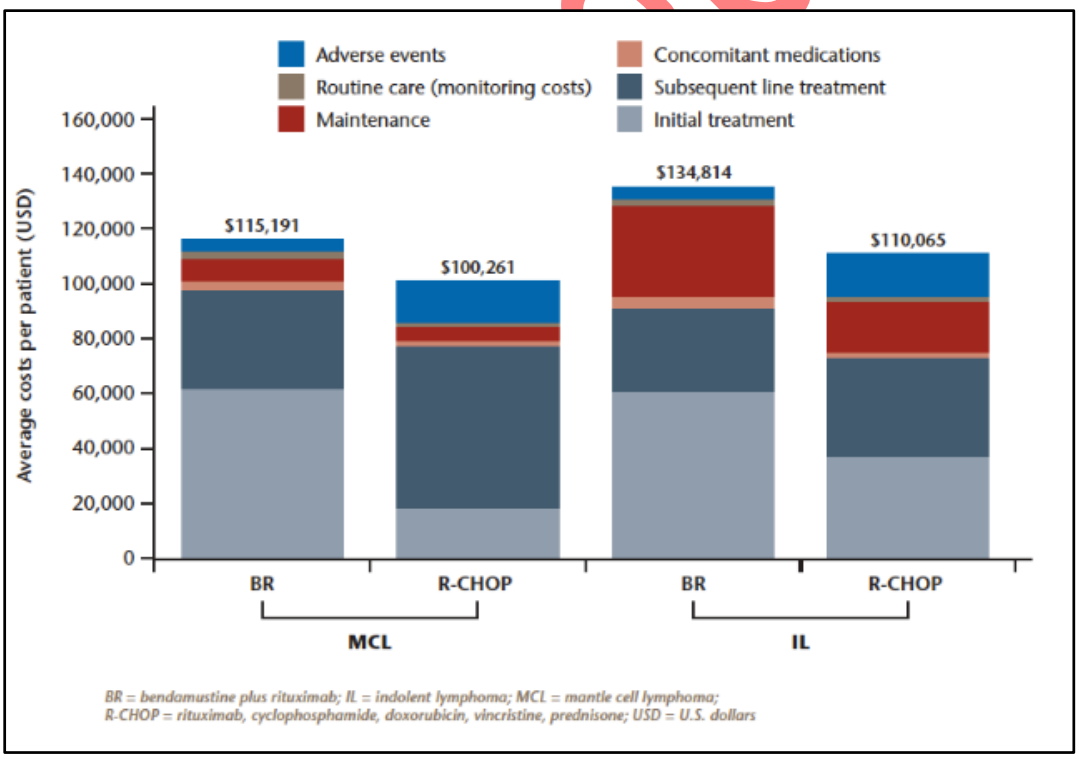
Geography	% of NHL	Details	Source
US	6.5%	3-10% of NHL	SEER
US	6.0%	4% to 8% of NHL The annual percent change was 5.87%	Zhou Y et al, 2008
US	6.0%	6% of NHL	Skarbnik AP et al, 2015
EU	6.0%	2% to 10% of NHL	Smedby KE et al, 2011
EU	7.0%	7% of NHL	Lymphomation

Some data suggest a possible increase in MCL incidence over the last two decades, but the observation may also reflect improved diagnostics. The incidence of MCL increased at annual rate of 5.87% from 1992 to 2004, and was significantly higher in men, in Caucasians, and patients aged > or =50 years. Most patients were diagnosed with late-stage MCL, and there also were considerable geographic variations observed in incidence rate. *(Zhou Y et al, Cancer 2008; SEER; EUCAN; UN Population Database)*

Geography	Population - 2016	NHL incidence rate / 100,000	Incidence -2016	
			NHL	MCL
US	324,118,787	22.4	72,580	4,476
UK	65,111,143	16.8	10,939	711
Spain	46,064,604	12.1	5,574	362
Germany	80,682,351	13.5	10,892	708
Italy	59,801,004	18.0	10,764	700
France	64,668,129	16.5	10,670	694

3. Economic burden: There are few assessments of the cost burden associ-ated with MCL. One recent cost-effectiveness study, which used US payer data, showed that the average per-patient cost of bendamustine plus rituximab, and the average per-patient cost of the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen both exceeded $100,000

Mean per patient costs for MCL were $115,191 for BR compared with $100,261 for R-CHOP, respectively *(Su W, et al. ASCO 2012)*



4. Risk Factors: The development of MCL can be caused by multiple factors and their interplays

4.1. Immune competence and infectious agents: Immune suppression has been connected to the risk of developing aggressive lymphomas. Evidence has been accumulating from studies that involve medications suppressing the immune system.

Multiple viruses have been implicated in the development of NHL overall [18]. Examples include EBV (Epstein-Barr virus), T-cell leukemia/lymphoma virus, hepatitis C virus, HHV-8 (human herpesvirus-8), HBV (hepatitis B virus), and others. However, according to an InterLymph study, there is still a lack of solid evidence for the association between these viral agents and the risk of MCL.

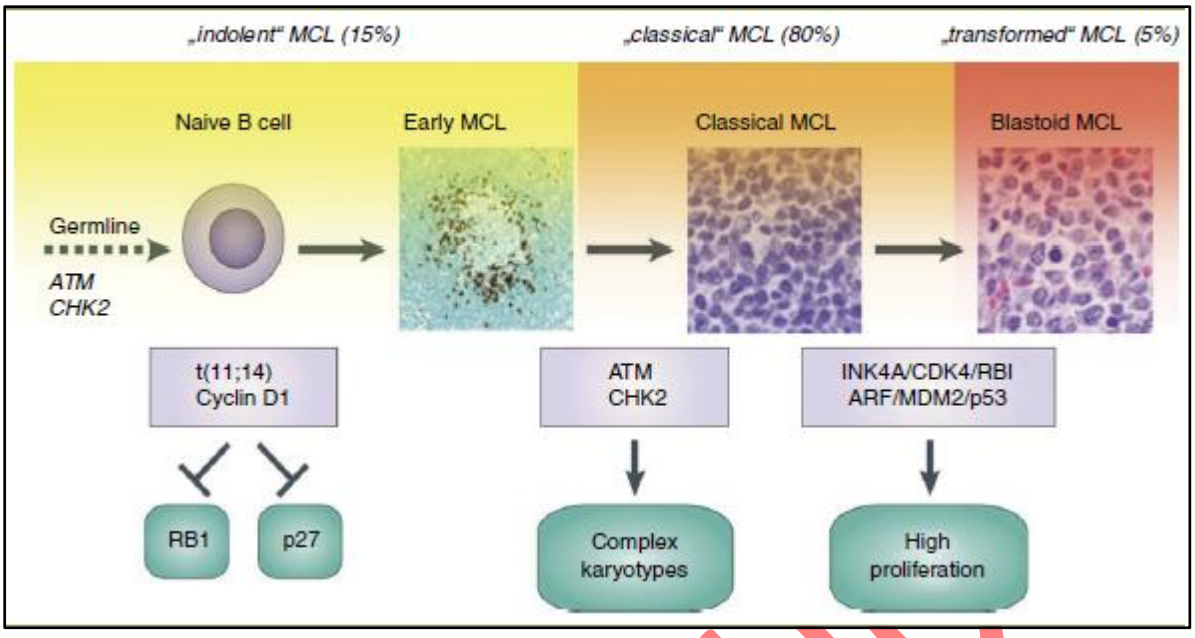
4.2 Family History: A family history of hematopoietic malignancies has been linked with a 2-fold increased risk of MCL, a magnitude similar to that for several other NHL subtypes such as DLBCL and FL but lower than that for CLL.

4.3 Molecular risk factors: Multiple types of molecular measurements have been implicated in cancer development. The genetic hallmark of MCL is the t(11;14)(q13;q32) translocation, which leads to the overexpression of CCND1.

- Gene CCND1 can deregulate cell cycle control by overcoming the suppressor effect of retinoblastoma 1(RB1) and the cell cycle inhibitor p27. Demonstration of CCND1 over-expression by immunohistochemistry or the t(11;14) (q13;q32) by molecular or cytogenetic methods has been critical in making a definitive diagnosis of most MCL cases
- Although the t(11;14)(q13;q32) translocation occurs in the majority of MCL cases, there have been reports of a small subset of tumors that do not overexpress CCND1 or in which the t(11;14)(q13;q32) is absent

In addition to the t(11;14)(q13;q32) translocation, MCL tumor cells may carry a large number of secondary chromosomal and molecular alterations targeting proteins that regulate the cell cycle and senescence (BMI1, INK4a, ARF, CDK4, and RB1) and interfere with the cellular response to DNA damage *(Wang et al ERH 2014).*

5. Diagnosis and Pathology/Molecular Biology: The diagnosis of mantle cell lymphoma (MCL) is established according to the criteria of the WHO classification of hematologic neoplasms. In general, histologic confirmation of diagnosis is mandatory and a lymph node biopsy is strongly recommended; in contrast, lymph node fine-needle biopsy is not appropriate. A bone marrow aspiration complemented by flow cytometry are mandatory to quantify the percentage of infiltration and optionally identify the pathognomonic t(11;14) by fluorescence in situ hybridization



Most tumors have a classic morphology of small to medium sized cells with irregular nuclei, dense chromatin, and unapparent nucleoli. In addition, a blastoid variant of the disease has been described, characterized by high mitotic rate and particularly aggressive behavior, which is associated with INK4a/ARF deletions and TP53 mutations. However, tumor cells may present with a spectrum of morphologic variants, raising some difficulties in the differential diagnosis apart from chronic lymphocytic leukemia, marginal zone lymphomas, large B-cell lymphomas, or blastic hematologic proliferations *(Pedro Jares et al, Nature Reviews Cancer 2007).*

Besides the classical immunophenotype (immunoglobulin M/D, CD19, CD20, CD22, CD43, CD79a, CD5 positive, and CD23, CD10, CD200, BCL6 usually negative), the detection of cyclin D1 overexpression (immunohistochemistry) or the chromosomal translocation t(11;14) by fluorescence in situ hybridization is mandatory, since histomorphologic phenotypes may differ significantly. Nevertheless, rare cases of cyclin D1-negative variant of MCL have been recognized, characterized by the same gene expression profile and secondary genomic alterations as classical MCL. SOX11, a transcription factor expressed in 90% of MCL, might be helpful to identify these cyclin D1-negative variants. Moreover, Ki67 proliferative index staining is strongly recommended as a powerful prognostic indicator of long-term outcome *(Martin Dreyling, ASCO)*.

6. Staging: To define the stage of MCL, a CT scan with iodine contrast of the neck, chest, abdomen, and pelvis is mandatory *(Dreyling et al, Annals of Oncology 2014)*

- Staging of NHL is established according to the Ann Arbor system

Stage	Area of Involvement
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both side of diaphragm

IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk >10cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms: weight loss >10%, fever, drenching night sweats

- For prognostic purposes, International Prognostic Index (IPI) and age-adjusted IPI (aa-IPI) are calculated
  - Each poor prognostic factor is assigned 1 point. People with no poor prognostic factors would have a score of 0, while those with all poor prognostic factors would have a score of 5. The index divides people with lymphomas into 4 risk groups: low, low intermediate, high intermediate, and high

International Index, All Pts	
Low	0 or 1
Low intermediate	2
High intermediate	3
High	4 or 5

- The IPI and aa-IPI are used to identify specific groups of pts who are more or less likely to be cured with standard therapy

International Index, Pts ≤60 years	
Low	0
Low intermediate	1
High intermediate	2
High	3

7. Treatment: Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes owing to the incurability of disease with conventional chemotherapy and a more aggressive disease course *(NCCN Version 2.2016)*

7.1 First line therapy: Stage I-II: In the small proportion of patients with limited non bulky stages I–II, radiotherapy (involved field, 30–36 Gy) has been suggested to achieve long-term remissions. In stage I–II patients with large tumour burden or adverse prognostic features, systemic therapy as indicated for advanced stages would be appropriate in most cases; a radiation consolidation may be considered, depending on tumour location and anticipated side-effects.

Stage III-IV: Rituximab in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine should be used. Rituximab maintenance significantly improves PFS and even OS after R-

CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) (75% versus 58% after 3 years)

Drug Regimen and FDA Approval Status	Efficacy Benchmarks	Grade 3/4 AE
1L		
Rituximab-CHOP (Not FDA approved)	• ORR: 94% • CR: 34% • mTTF: 21 mos • mPFS: 18 mos • OS3 Yrs: 75%	• Anemia: 9% • Leukocytopenia: 69% • Granulocytopenia: 63%
2L		
Bortezomib US FDA Approved (December 2006) for relapsed MCL in pts who have received at least one prior therapy	• ORR: 32% • CR: 8% • mDoR: 9.2 mos • mTTP: 6.7 mos • mPFS: 6.5 mos • mOS: 23.5 mos	• Peripheral neuropathy:13% • Lymphopenia: 34% • Thrombocytopenia: 11% • Fatigue: 12%
Ibrutinib US FDA Approved (November 2013) for Relapsed MCL, pts who have received at least one prior therapy	▪ DoR: 17.5 mos ▪ mPFS: 13.9 mos ▪ OS_{18mos} : 58%	• Neutropenia (16%), • Thrombocytopenia (11%) • Anemia (in 10%)
3L		
Lenalidomide US FDA Approved (June 2013) for MCL whose disease has relapsed or progressed after two prior therapies, one of which included Bortezomib	• ORR: 28% • CR/uCR: 8% • PR: 19% • DoR: 16.6 mos • mPFS: 4.0 mos	• Neutropenia: 43% • Thrombocytopenia: 27% • Anemia: 11% • Flare reaction: 10%

(ORR- Oveall Response Rate, CR- Complete Response, PR- Partial Response DoR- Duration of Response, TTP- Time to Progression, PFS- Progression Free Survival, OS- Overall Survival)

7.2 Second or Third line therapy (Relapsed/Refractory): Selection of salvage treatment depends on efficacy of prior regimens. Bortezomib and Ibrutinib are currently being used as the second line therapy for the treatment of MCL, while Lenalidomide is used as the third line therapy *(Dreyling et al, Annals of Oncology 2014)*

8. Unmet Need: a) Aggressive and incurable**:** MCL is considered as an aggressive and incurable B-cell malignancy despite current available treatments that include the incorporation of rituximab, bortezomib, high-dose cytarabine, and for those eligible, high dose chemotherapy and autologous bone marrow transplant

b) Need for new and safe treatment options: Few treatment options are available to mantle cell patients. Autologous stem cell transplants or aggressive immuno chemotherapies have significant toxicity and mortality risks

c) Fewer options for relapsed or refractory MCL: Despite high response rates with current 1st Line treatments, most patients eventually relapse and become typically chemo resistant, leading to very poor outcome *(Goy et al. Hematology 2011)*

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