Mantle Cell Lymphoma (MCL)

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Here you will find comprehensive information on classification, diagnosis, prognosis and therapy in mantle cell lymphoma (MCL).

Diagnostic Recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	mandatory
Chromosome analysis	Heparin	optional
FISH	EDTA or Heparin	mandatory
Molecular genetics	EDTA or Heparin	optional

Definition and characteristics of Mantle cell lymphoma

Mantle cell lymphomas (MCL) account for approximately 3-10% of all non-Hodgkin lymphomas. The median age at diagnosis is about 60 years. Men develop the disease more than twice as often as women. The **MIPI** (MCL International Prognostic Index) has been established as a clinical risk score. The MIPI is based on parameters such as general health, age of the patient, LDH and leukocyte values. By using the MIPI, patients with mantle cell lymphoma can be divided into three risk groups: low, intermediate and high. As an additional parameter, the index of the proliferation marker Ki-67 can be used, which is considered a risk factor in its own right. In combination, the MIPI and Ki-67 index form the MIPI-c *(combined MIPI)* for risk assessment. Genetically, mantle cell lymphoma can be characterized by *CCND1* translocations, classically t(11;14)(q13;32), leading to overexpression of cyclin D1 (*CCND1*) (Hoster et al. 2008, Hoster et al. 2016, Swerdlow et al. 2017).

Classification of mantle cell lymphoma

Mantle cell lymphoma (MCL) is classically a B-cell neoplasm with indolent to aggressive courses that develops linearly from naïve B cells. Indolent variants include leukemic non-nodal mantle cell lymphoma and in situ mantle cell neoplasia (ISMCN). According to the new 2017 WHO classification (Swerdlow et al. 2017), mantle cell lymphoma (MCL) is divided into two subtypes according to clinicopathologic features and underlying pathogenic pathways:

- Classical mantle cell lymphoma with unmutated/minimally mutated IGHV and *SOX11*-positive.
- Non-nodal mantle cell lymphoma with mutated IGHV and *SOX11*- negative

SOX11-negative mantle cell lymphoma is the much rarer variant and accounts for approximately 14%-32% of mantle cell lymphoma. Genetically, this form of mantle cell lymphoma is more stable than *SOX11*-positive MCL. The *SOX11* gene encodes the transcription factor *SOX11*, which is not expressed in normal B cells and in mantle cell lymphoma influences B cell differentiation, proliferation, and apoptosis, among other functions (Cheah et al. 2016, Martin 2018, Puente et al. 2018).

Classical vs. non-nodal mantle cell lymphoma
In the pathogenesis of classical mantle cell lymphoma, progenitor B cells, in which a *CCND1* rearrangement is usually present, mature into naïve B cells with genetic abnormalities that initially settle in the inner region of the mantle zone of lymphoid tissue and usually have no or minimal IGHV mutations and are *SOX11*-positive. Without transit through the germinal center, classic mantle cell lymphoma affects both lymph nodes and extranodal sites. During progression, blastic and pleomorphic variants of mantle cell lymphoma may develop (see Cytomorphology). A commonly aberrant gene is TP53 (localized to 17p13), which encodes a tumor suppressor protein and is involved in a number of processes including apoptosis and cell differentiation. Abnormalities of this gene are typical of genetically unstable diseases. Reduced expression of wild-type TP53 and expression of mutant *TP53* result in loss of growth-limiting function of the gene. Abnormalities of TP53 are associated with lower response to therapies as well as shortened overall survival, with mutations having even greater relevance here than deletions (Greiner et al. 1996, Dreyling et al. 1997, Greiner et al. 2006, Halldórsdóttir et al. 2011, Eskelund et al. 2017, Swerdlow et al. 2017).

17p deletions leading to *TP53* gene loss and *TP53* mutations are found in both classical and non-nodal mantle cell lymphoma. Biallelic inactivation can occur when mutation and deletion are present simultaneously; this is also observed in both subtypes (Clot et al. 2018, Nadeu et al. 2020).

Leukemic non-nodal mantle cell lymphoma differs from classical mantle cell lymphoma in the absence of significant adenopathy. The neoplastic cells of non-nodal MCL are usually small, resemble those of **chronic lymphocytic leukemia (CLL)**, are *SOX11* negative, and have somatic IG hypermutations that presumably arise during germinal center transit. Non-nodal mantle cell lymphoma often involve the peripheral blood, bone marrow, or spleen. They are genetically more stable and have few additional aberrations to the *CCND1* translocation, del(17p), and TP53 mutations. Prognosis for overall survival is generally better than for classic mantle cell lymphoma (median survival 68 months), with a median survival of 79 months, and the time to initial therapy is also longer. However, non-nodal mantle cell lymphoma can also evolve into aggressive disease, which is often associated with the presence of *TP53* mutations or other oncogenic abnormalities (Swerdlow et al. 2017, Clot et al. 2018, Maddocks 2018, Sander 2020). In clinical practice, distinguishing between the two subtypes is challenging despite the different abnormalities (Martin 2018).

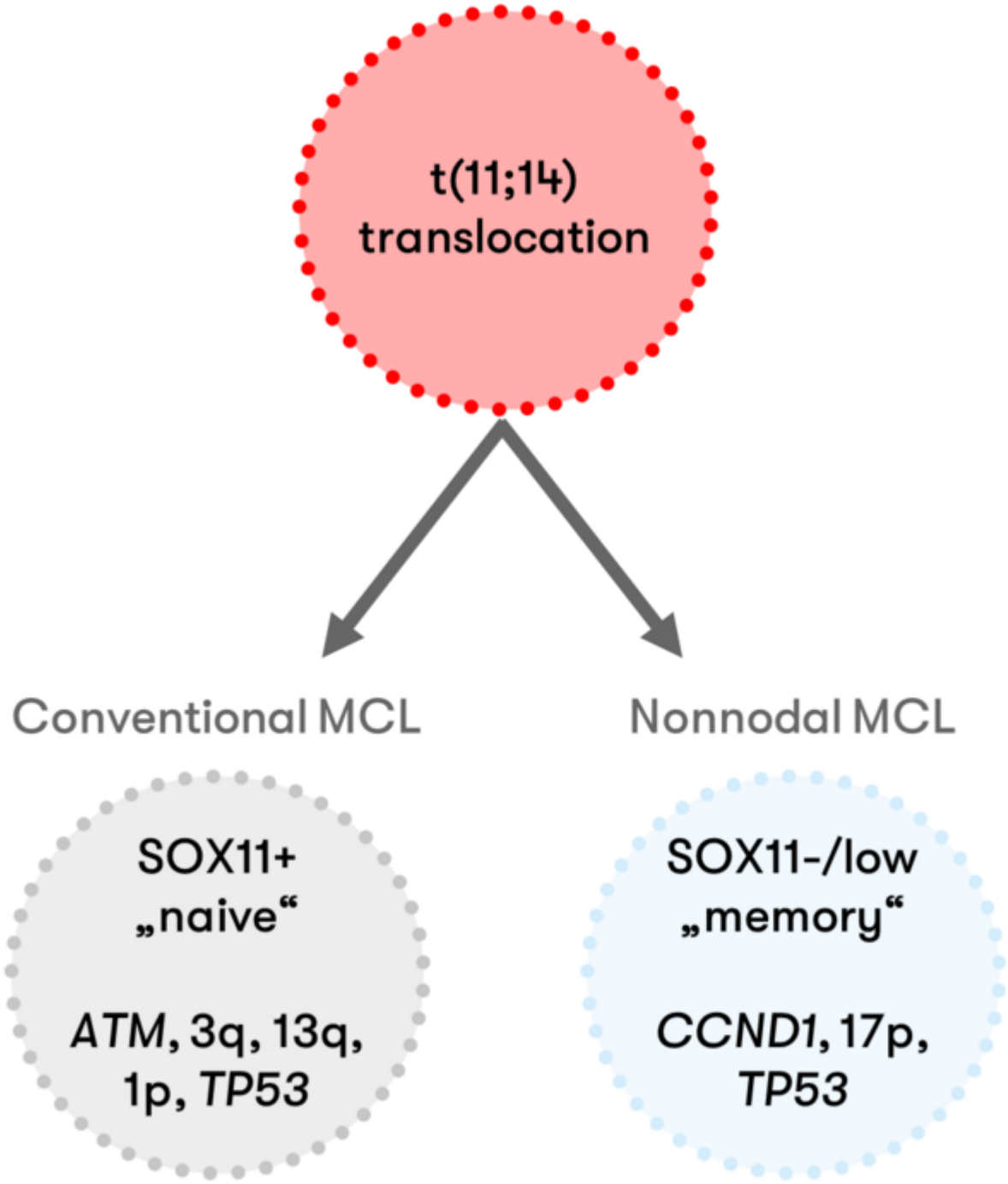

Fig. 1: Distinction between classical and non-nodal mantle cell lymphomas (modeled after Sander 2020).
Classical MCL typically show high *SOX11* expression, mutations of the *ATM* and *TP53* genes, copy number gains of 3q, and copy number losses of 13q and 1p. Non-nodal MCL typically show no or low *SOX11* expression, mutations of the *CCND1* and *TP53* genes, and copy number losses of 17p.

In Situ Mantle Cell Neoplasms
In addition to classic and non-nodal MCL, there are in situ mantle cell neoplasms characterized by the presence of *CCND1*-positive lymphoma cells, with the presence of *CCND1* rearrangements restricted to cells in the mantle zone of otherwise hyperplastic lymphoid tissue. *CCND1*-positive cells are typically found in the inner mantle zone. Compared with classic MCL, in situ mantle cell neoplasms are more often CD5-negative. Both *SOX11*-positive and *SOX11*-negative cases have been reported, with the latter being much less common. In situ mantle cell neoplasms often show an indolent course, but in rare cases can also develop into mantle cell lymphomas (Swerdlow et al. 2017).

Diagnostics of mantle cell lymphoma

Cytomorphology

In diagnostics, assessment of the blood and bone marrow smear provides an initial landmark statement as to whether lymphoma washout exists or is possible. In addition, cytomorphology and histology are useful in assessing the maturity of mantle cell lymphoma.

According to the 2017 WHO classification, there are clinically aggressive morphologic variants that can develop from classic mantle cell lymphoma , which include blastic and pleomorphic variants. High proliferation rates are characteristic of both variants. The lymphoma cells of the pleomorphic variant are larger than those of a classic mantle cell lymphoma, and the shape of the nucleus and chromatin structure resemble those of diffuse large B-cell lymphoma (DLBCL). In addition, the cytoplasm is usually pale and the nucleus contours are irregular. The blastic variant resembles lymphoblasts and shows roundish nuclei, a high mitotic rate, a narrow cytoplasmic rim, and scattered chromatin (Swerdlow et al. 2017, Dreyling et al. 2018).

In addition, cytomorphology reveals small-cell mantle cell lymphoma ('small-cell') and marginal zone-like mantle cell lymphoma as further variants (Swerdlow et al. 2017).

Immunophenotyping

In the case of lymphomas, such as mantle cell lymphoma, immunophenotyping allows clear determination of lineage affiliation to the T or B lineage, or precise differentiation of lymphomas. Furthermore, multiparametric flow cytometry is often indispensable for differentiating a reactive change from a lymphoid neoplasm, e.g. in EBV infections.

Mantle cell lymphomas express CD5 and are usually negative for CD23 in contrast to B-CLL. Table 1 shows characteristic findings in mantle cell lymphoma.

Table 1: Immunophenotyping in mantle cell lymphoma (after Béné et al. 2011).

Antigene	Markers
CD19	+
CD20	+
CD22	+
CD23	-
CD25	-
FMC7	+(-)
CD79b	+
CD5	+
sIg	+
CD10	-
CD11c	-
CD103	-
CD43	+

Chromosome analysis

Translocation t(11;14)(q13;q32) is characteristic in mantle cell lymphoma

Characteristic in mantle cell lymphoma is the translocation t(11;14)(q13;q32) leading to an IGH-CyclinD1 (*CCND1*) rearrangement. Instead of an IGH-*CCND1* rearrangement, variants also occur in which the light chains of the immunoglobulins IGK or IGL are involved in a rearrangement with *CCND1*. In addition, rearrangements involving *CCND2* (12p13) or *CCND3* (6p21) occur very rarely. Frequently, additional cytogenetic abnormalities are found, some of which are complex (see list below) (Espinet et al. 2010, Cohen 2017, Swerdlow et al. 2017).

Cytogenetic abnormalities in mantle cell lymphomas.

Balanced translocations:
t(11;14)(q13;q32)/IGH-*CCND1*, t(2;11)(p11;q13)/IGK, t(11;22)(q13;q11)/IGL
less frequently: t(8;14)(q24;q32)/IGH-*MYC*, 3q27/*BCL6* rearrangements

Gains:
3q, 7p, 8q, 11q, trisomy 12, 13q, 15q, 18q, tetraploid chromosome set

Losses:
1p, 6q, 8p, 9p, 11q, 13q, 17p, Y

FISH

With the help of FISH analysis, chromosomal regions with genetic alterations can be detected, such as the characteristic IGH-*CCND1* translocation, whereby FISH analysis can help to confirm the diagnosis (Espinet et al. 2010). Additional alterations can often be detected in chromosomal regions where the *ATM* (11q22-q23), *CDKN2A* (9p21), or TP53 (17p13) genes, among others, are located (Sander et al. 2008). *TP53* and *CDKN2A* deletions are associated with an unfavorable prognosis, with an additive prognostically unfavorable effect when both deletions occur (Delfau-Larue et al. 2015).

Molecular genetics

CyclinD1 (*CCND1*) overexpression characteristic of mantle cell lymphoma.
At the molecular level, mantle cell lymphoma is best confirmed by measuring cyclinD1 (*CCND1*) overexpression. In addition, detection of the IGH-*CCND1* rearrangement (also IGH-*BCL1* rearrangement) ias possible (Swerdlow et al. 2017). However, only about 40% of all IGH-*CCND1* rearrangements can be detected by PCR due to breakpoint heterogeneity (Belaud-Rotureau et al. 2002).

***SOX11* expression**
As an additional marker, especially for *CCND1*-negative mantle cell lymphomas, *SOX11* expression can be determined (Royo et al. 2011). The prognostic relevance of *SOX11* overexpression is currently controversial. Results of a study on classical and indolent MCL could show that *SOX11* overexpression has a prognostic negative impact on disease progression (Fernàndez et al. 2010). A reduced time to treatment indication was also found in patients with *SOX11* expression (Meggendorfer et al. 2013). In contrast, various studies have also described a more indolent clinical picture in patients with *SOX11* expression and a shorter overall survival in *SOX11*-negative patients (Wang et al. 2008, Nygren et al. 2012, Meggendorfer et al. 2013).

Recurrent mutations
Some patients have clinically relevant mutations in the *ATM*, *TP53*, or *NOTCH1/2* genes. *ATM* (40-75%) and *CCND1* (35%) represent the most commonly affected gene loci (Beà et al. 2013, Swerdlow et al. 2017). *ATM* mutations are often accompanied by structural and numerical chromosomal alterations (Salaverria et al. 2008). In turn, inactivation of *ATM* appears to lead to telomere shortening, which may contribute to structural genomic complexity (Nadeu et al. 2020). Mutations in exon 58 of the *UBR5* gene are also detected in 18% of patients with mantle cell lymphoma (Meissner et al. 2013). Mutations in *NOTCH1/2* are of prognostic and potential therapeutic importance (Swerdlow et al. 2017).

Molecular markers in MCL:
- *IGH-CCND1*
- *CCND1 overexpression*
- *SOX11*
- *UBR5*
- *TP53*
- *ATM*
- *NOTCH1/2*

In addition to these molecular markers, mutations in additional genes have been found in several studies (Cheah et al. 2016, Hill et al. 2020). Nadeu et al. were also able to identify additional driver mutations involved in various mechanisms relevant to the pathogenesis of mantle cell lymphoma (*CDKN1B*, *SAMHD1*, *HNRNPH1*, *SMARCB1*). Among these, more driver mutations and, most importantly, more numerical and structural abnormalities were found in the more aggressive classical mantle cell lymphoma than in non-nodal mantle cell lymphoma, in which only *TERT* and *TP53* were more frequently mutated (Nadeu et al. 2020).

Classical and blastic mantle cell lymphoma show similar genetic alterations. In particular, *TP53* mutations with high expression levels of the associated protein appear to be common in blastic mantle cell lymphoma and play a strong prognostic role. *NOTCH1/2* mutations are also clustered in blastic mantle cell lymphoma . Genetic abnormalities appear to have an impact on the evolution of classic mantle cell lymphoma into a more aggressive variant. In this context, the increase in abnormalities is thought to lead to a loss of cell cycle control, as well as increased proliferation rate and blastic characteristics (Dreyling et al. 2018).

In a study by Clot et al, the distinction between a classical and non-nodal mantle cell lymphoma was performed using an RNA gene expression assay in peripheral blood lymphoma cells (L-MCL16 assay), clearly defining the two molecular subtypes. In addition, sequencing was performed for molecular characterization. The combination of the two methods could contribute to treatment decisions; however, the small number of lymphoma cells could cause problems in patients with minimal disease burden or in the early stages (Clot et al. 2018, Martin 2018).

Prognosis

Patients with a *TP53* deletion (17p deletion) or a *CDKN2A* deletion (9p deletion) have a less favorable prognosis independent of the proliferation marker Ki-67 and the risk score MIPI (Rubio-Moscardo et al. 2005, Salaverria et al. 2007, Sander et al. 2008). Eskelund et al. demonstrated that patients with age less than 65 years and *TP53* mutation have significantly reduced overall survival and progression-free survival compared with patients with TP53 deletion or without *TP53* abnormalities, as well as a significantly increased risk of recurrence. In addition, *TP53* mutations appear to be frequently associated with blastoid morphology, Ki67 scores of > 30%, high MIPI score, and high MIPI-c risk (Eskelund et al. 2017). When *TP53* and *CDKN2A* deletion occur simultaneously, there is an additive prognostically unfavorable effect. The prognosis of patients with heterozygous *CDKN2A* deletion does not differ from patients with homozygous *CDKN2A* deletion (Delfau-Larue et al. 2015).

Mutations of *NOTCH1/2* are associated with an aggressive clinical course and occur in approximately 5-10% of mantle cell lymphoma (Cheah et al. 2016).

The proliferation marker Ki-67 also serves as an independent prognostic marker. An increased rate of Ki-67-positive tumor cells is associated with shorter overall survival and progression-free survival (Hoster et al. 2016).

While non-nodal mantle cell lymphoma generally has a more favorable prognosis than classical mantle cell lymphoma (see also Classification), the survival benefit was found to be strongly dependent on the number of copy number alterations (CNA). Here, more than 6 CNA in both classical and non-noda mantle cell lymphoma lead to significantly shorter overall survival compared to a number of 0-5 CNA (Clot et al. 2018). This may also have relevance for the treatment of patients in the future (Martin 2018).

Calculation of prognosis
Click here for the prognosis calculation of the **MIPI score**.

Therapy

Response to standard chemotherapy and autologous stem cell therapy may be influenced by molecular mutations. Patients with an age below 65 years and *TP53* mutation were less likely to achieve complete remission after induction chemotherapy or autologous stem cell therapy in a study by Eskelund et al. Therefore, mutation status may play a role in treatment decisions (Eskelund et al. 2017). When choosing therapy, both chemotherapies and non-chemotherapies or combinations may be considered, and their respective benefits should be assessed in context with mutation status (Martin et al. 2017). According to the current **Onkopedia guideline on mantle cell lymphoma**, patients with indolent lymphomas should be treated in the setting of clinical trials whenever possible. This is especially true for patients with a high burden of copy number alterations (Martin 2018).

Recommendation

According to the current **Onkopedia guideline on mantle cell lymphoma**, in addition to the collection of clinical and laboratory parameters from peripheral blood (cell count, differential blood count, reticulocyte ESR, electrophoresis, total protein, GOT, GPT, AP, γ-GT, bilirubin, creatinine, uric acid, blood glucose, LDH, β^2-microglobulin, Quick value, PTT) a cytological and histological examination of the bone marrow is recommended, in case of leukemic course also FACS analysis of surface markers from peripheral blood.

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/mature-b-cell-neoplasms/mantle-cell-lymphoma-mcl.html#referenzen