In last several decades, we have seen great advance in all lymphoma treatment. The significant progress was made in treatment of many B-cell lymphomas with introduction of purine analogs like fludarabine, monoclonal antibodies like rituximab, and high dose chemotherapy with autologous stem cell transplantation. That improved treatment of chronic lymphocytic leukemia, small lymphocytic, marginal zone, follicular or even diffuse large B-cell lymphoma. Unfortunately, this success was less prominent in entities like mantle cell NHL (MCL) and in T-cell NHL.

Our aim was is to summarize our knowledge of biology and treatment of MCL and to make a critical evaluation of possible treatment of MCL in Balkan countries.

**Biology and origin of Mantle cell lymphoma**

In last decades, there are many controversies concerning this type of lymphoma, separating it from spectrum of small lymphocyte neoplasm. First reports by Wiesenburger in 80’s (1,2) led to introduction of the term MCL by Lymphoma study group (2) in 1992 describing this entity in further classifications up to WHO 2008 (1-3).

MCL is mature B-cell neoplasm, arising from naive pregerminal B-cells in inner mantle area of lymph follicle. In neoplastic transformation, those cells develop unique genetic alterations affecting genes responsible for cell cycle like Cyclin D1 and IGH region. Almost all patients carry t(11;14) (q13;q32), deregulating CCDN1 region responsible for cyclin D1 and this is considered as primary genetic event, or in some rare cases the deregulation of Cyclin D2/D3 in cases with t(2;12), t(12;14), t(6;14) (3,4). This leads to cyclin overexpression, and genomic instability affecting not only B-cell receptor biology (BCR) but also make alterations in many downstream regulatory pathways like cell cycle control, DNA damage control pathway and p53/MDM genes, as well PI3/AKT, mTOR, NF-kB and apoptosis regulators like bcl-2 family (3,4). Moreover, many other changes are present, especially in microenvironment (Burger) where tumor associated macrophages and stromal cells can help further cytokine stimulation of neoplastic lymphocytes through cytokine kinase receptors (5).

**Clinical characteristics**

MCL is not fast growing lymphoma, but at diagnosis many patients have advanced disease or leukemic phase (3,6,7). According to several reports, leukemic phase can be detected at diagnosis in one fourth of patients (3,7), but in our series is present in 2/3 of patients (6). Sometimes, the leukemic phase of disease can make a diagnostic challenge. Bone marrow infiltration is frequent and according to reviews, it is present in almost 2/3 of cases (7,8). Besides, extranodal involvement, particularly involvement of sinuses and Waldeyer ring or digestive system is common. In any part of digestive system, MCL infiltration can form multiple lymphomatous polyps (1,7). Other extranodal propagations are not frequent but sometimes MCL can infiltrate ocular area (9) or skin.

**Diagnosis and pitfalls**

Early detected, in lymph node, mantle expansion of follicles and nodular growth pattern could be seen, but in advanced disease at diagnosis, diffuse growth pattern is more frequent (3/4 of cases) (1,2,7).
MCL in general has monotonous morphology, consisting of similar cells. There are several morphological types of MCL cytology which can be detected on bone marrow smears, but also on lymph node of bone marrow biopsies. The typical MCL morphology is a small to medium sized cell with irregular nucleus, with speckled or slightly open chromatin and small inconspicuous nucleolus, sometimes with indentations of nucleus called “fish mouth” (1,2). Aggressive variants are blastic and pleomorphic. Blastoid variant of MCL is characterized by cells resembling lymphoblasts with dispersed chromatin and high mitotic or proliferation rate (1). In our series (6) blastic variant was present in 20% of cases like in other reports (1,7,8). Pleomorphic variant is also aggressive one, characterized by cell pleomorphism, and domination of large cells with oval or irregular nuclear outline, pale cytoplasm and prominent nucleoli. Two other variants are less aggressive in biological behavior. These are small cell MCL characterized by small round lymphocytes, with frequently clumped chromatin, and with rare larger cells, and in some cases it is difficult to discriminate those cells from lymphocytes in pleomorphic form of CLL (10). This small cell type was seen in 10% of cases in our series (6). Marginal zone-like MCL is also rare variant with cells showing abundant pale cytoplasm, similar to marginal zone or monocytoid B-cells.

In diagnostic workup, it should be noted that biopsies of all affected tissue are essential, and not only imaging procedures. Bone marrow infiltration pattern is in general diffuse and additional immunophenotyping on bone marrow should be helpful.

Immunophenotype of mantle cells is specific to certain extent but also have much in common with CD5+ CLL. Mantle B-cells are B-cell positive (CD19, CD20, CD22, CD79a, PAX5), and also CD5+. Unlike B-CLL, mantle cells are strongly CD20+, FMC7+ and sIgM/sIgD+ and generally CD23 negative. Also MCL cells are Bcl-2+ in almost all cases, but CD10 and Bcl-6 negative. The main hallmark in diagnostic procedure is to detect overexpression of Cyclin D1 by immunohistochemistry.

Figure  Morphology of MCL (bone marrow biopsy, aspirate and Cyclin D1 IHC, phenotype)
The widespread use of biological proliferation marker, Ki-67 as prognostic tool in MCL (1,13). Patients with high Ki-67 (>40%) have worse outcome. Both clinical derived indices like MIPI and Ki-67 should need further evaluation for applicability in patients treated with intensive immunochemotherapy but their use are strongly recommended by ESMO (14).

Frontline treatment

Since early stage disease is rare, many reports target in general treatment of advanced phase disease, and further “salvage” treatments. There is another problem in efficient treatment of MCL patients, the age of patients. In many reports, it is shown that average patient with mantle cell is predominantly male in fifth or sixth decade of life and significant proportion of patients have more than 60y of age (77%) (8). These data opens the issue of role of intensive chemotherapy in treatment of this aggressive lymphoma.

Many chemotherapeutic regimens were tried in treatment of MCL (7,12,14). Several trials revealed that overall response rate of CHOP and CHOP based chemotherapy can achieve overall response rate of about 75% (12,14). Unfortunately, all studies short time to treatment failure and also short survival (TTF was 14 months, and 2y OS of 60-70%).
Several combination regimens were used, like fludarabine based rituximab containing protocols (R-FMC or R-FMD), rituximab and bendamustin schedules (7,12).

Specific biology of MCL and downstream activation of many pathways open the new field in secondary treatment. Several new agents are proposed for treatment of patients in relapse, and two of them received approval in EU or USA for treatment of relapsing MCL.

Bortezomib is proteasome inhibitor with antineoplastic action on several levels. The main pathway is to block proteasome activity and to suppress NFkB pathway. Also, bortezomib have the activity towards NOXA, proapoptotic member of Bcl-2 family of regulators, inducing cell death. Probably, bortezomib also have several other mechanism of action like disruption of neovascularization, and stabilization of p52 and JNK (17). As single agent, bortezomib was used in several trials in USA, in patients with previously treated MCL. In doses of 1.3 mg/m2, bortezomib alone had overall response rate of 32% and in combination with chemotherapy, response rates were better 46% (14,18). Afterwards, US FDA approved bortezomib as a second line drug in USA. Unfortunately, PFS is quite short, about 6-9 months (14) and therefore level of evidence nowadays is IIIB (14). Further status of bortezomib should be determined in combination therapy and findings of future randomized trial.

Temsirolimus and mTOR inhibitors are compounds directed towards inhibition of mTOR pathway. The exact mechanism for action of temsirolimus and other mTOR inhibitors is unknown, but in experimental settings, it is shown that those compounds block cell cycle, through G0/G1 arrest, induce and block autophagy, and induce apoptosis. Also, mTOR inhibitors down regulates cyclin inhibitors like p21 (19-21). There is also evidence that mTOR inhibition by temsirolimus can down regulate cyclin D1 expression (19). All that led to several clinical trials with temsirolimus and everolimus in patients with MCL. Overall response rate in trials was 38-41% (14,21), and the addition of rituximab showed more encouraging result with response rate of 60%. Those results, led to registration of temsirolimus as monotherapy in EU for patients with MCL with level of evidence IIB (14).

Lenalidomide. Due to its immune modulatory and antineoplastic action, lenalidomide was also tried in relapsed MCL. In refractory MCL it showed large meta-analysis of patients treated with rituximab based imunochemotherapy for lymphoma (predominantly R-CHOP) (12,14,16), revealed that addition of rituximab significantly improves general treatment outcomes in MCL as well in other indolent lymphoma. Therefore, ESMO in 2013 recommended R-CHOP regimen as mainstay treatment in elderly fit patients with MCL. With addition of Rituximab the overall response rate rise to 94% vs. 75%, complete remission rate was improved to 34% vs. 7%, and also overall survival was improved, about 60-70 months (16). Moreover, ESMO recommend rituximab maintenance, one dose on two months in all responding patients up to relapse. This regimen in a controlled trial provided significant advantage in longer remission and also in longer survival (87% of OS at 4 years, and 57% patients still in remission at 4 years) (16).

Similar treatment may improve treatment outcomes in younger fit patients with MCL, but subsequent trials with intensified regimens consisting of blocks of cytosine arabinoside and/or metotrexate as intensification revealed that overall outcomes in younger patients are much better. That leaded the introduction of HyperCVAD chemotherapy together with AraC and metotrexate with rituximab as the “standard” of care in younger patients (14,16). The overall response rate is about 80-90% and complete remission rate is about 60-70%, but also with significant hematological toxicity and infections. 3 year failure free survival was about 60-65% and 3 year overall survival was about 80%. Therefore, ESMO recommends addition of rituximab to chemotherapy like CHOP or better like HyperCVAD to all MCL patients available for full treatment (16). Also ESMO in last proposals in 2013 recommend autologous stem cell grafting with intensive treatment during conditioning as the best way to treat younger patients. All those recommendations are I A or B. Unfortunately there is no clear difference in type of conditioning for transplantation (16). Moreover, recently MCL Network, decided to recommend also similar combination chemotherapy, R-CHOPx3 and R-DHAPx3 as better tolerated regimen (14,16).

“Salvage” or second Treatment

Mantle cell lymphoma have high rate of recurrence, and almost 50-60% of patients relapse within period of 5 years. Due to intensive treatment, especially in younger patients, it is difficult to have any recommendation towards treatment.
overall response rate of 42%, and good long term outcome in responding MCL. Unfortunately, myelosuppression was moderate. Therefore, further clinical evaluation of this drug is needed (14).

Several other compounds are under investigation, acting on several levels. The promising target is disruption of regulatory pathways from B-cell receptor and downstream signaling (22,23). In these pathways, the AKT/PI3 and Bruton kinase system are active. Several selective inhibitors of those proteins are in preclinical testing, with the aim to disrupt signaling from BCR, and also to disrupt gene activation (23-25).

**In conclusion**

Mantle cell lymphoma is still controversial disease, with different biological behavior. Our present knowledge led us towards effective frontline treatment, mainly with rituximab based chemotherapy and European Society for Medical Oncology recommended in 2013 R-CHOP and R-HyperCVAD/R-MTX-AraC as standard for all fit patients (12). They also recommended autologous stem cell grafting after achieving the first remission. This treatment can lead to overall survival of at least 6 to 8 years in about one third to one half of the patients depending on MIPI score and biological variables like blastoid cell variant or high Ki-67 proliferative fraction. Unfortunately, most of MCL patients relapse and new agents are under way or are approved as monotherapy for salvaging patients.

In Balkan countries we can strongly support use of rituximab based regimens, by professional pressure towards regulators, since Rituximab use in this indication is “off label use” and therefore hematologists may have a prescription problems. Also, we strongly believe that in near future, new indications would be approved for bortezomib and temsirolimus, and will further help towards better treatment of patients with mantle cell lymphoma.

**References**


