E10. MANTLE CELL LYMPHOMA- DIAGNOSIS AND TREATMENT ACTUALITIES

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Mantle cell lymphoma (MCL) is a rare type of non-Hodgkin Lymphoma (NHL), representing about 7% of adult NHL. The median age of patients at presentation is around 65 years, with a male: female ratio of 3:1. The majority of MCL patients are diagnosed on advanced stages and about 1/3 have malignant lymphocytes in peripheral blood. Central nervous system involvement is rare and usually associates leukemic phase of disease. More than 1/3 of the patients have B symptoms at diagnosis and gastrointestinal tract involvement. From a histological point of view, malignant cells are small or medium monomorph B lymphocytes with irregular nuclei. Cells morphology could vary from small lymphocytes (centrocitic-like) to lymphoblast-like cells (blastoid variant). Mitotic index is higher than indolent lymphomas. The cells presents B cell immuno-phenotype: CD 19+, CD 20+, CD 5+, FMC 7+. Rarely, the cells culd be CD 5 – and CD 23+, associating a high surface IgM and IgD level. In 95% of the cases, D1 Cycline is positive, even in CD5 – cells. D1 Cycline could be used in differential diagnosis between MCL and indolent lymphomas like lymphocytic lymphoma, splenic marginal cell lymphoma, etc. D1 Cycline is negative in 5% of cases. 50-60% of cases are positive for t(11;14). Other chromosomal alterations (that associates c-myc mutation) are present in blastoid variant, frequently associated with poor prognosis.

Currently, there is no general consensus on the MCL treatment. Considering that some MCL patients, especially those with low International Prognostic Index (MIPI) score have an indolent clinical course for months to years, a watch-and-wait approach has been advocated for selected patients. In general, fit younger than 65 years patiernts without comorbidities are candidates for intensive chemotherapy (regimens based on high dose ARA-C) followed or not by stem cell transplant as consolidation. This strategy evolved from the fact that less intensive regimens (as CHOP or R-CHOP) produced only a modest benefit with median progression free survival of 16 months. All the studies proved a better outcome in patients treated with high doses ARA-C. As expected, intensive regimens were associated with significant toxicities, especially in older patients. The studies reported a complete remission (CR) rate of 87% using R-HyperCVAD/R-MTX-ARA-C regimen and of 61% using R-CHOP+ 3R-DHAP followed by autologus stem cell transplantation (ASCT). It is still not clear weather all patients should be offered ASCT because CR rates (after R-HyperCVAD and no ASCT) are similar with those who were transplanted.

In elderly patients who are not candidates for intensive therapy, the choice of therapy should take into account balancing clinical benefit with treatment related toxicities. R-HyperCVAD/R-MTX-ARA-C regimen is less beneficial in patients older than 65 years and also more toxic. Otherwise, R-CHOP regimen is relatively safe, but ineffective. Therefore, these patients are candidates for testing new regimens more efficient than CHOP. To improve progression free survival, maintenance strategy was explored, using Rituximab or α-Interferon. Rituximab is less toxic and more efficient than Interferon. Other treatment option was (1) R-HyperCVAD/R-MTX-ARA-C regimen without R-MTX/ARA-C alternance, followed by Rituximab maintenance. (2) R-Bendamustine associating Lenalidomida and Ofatumumab. Regimens containing Fludarabine were not efficient and hematologic toxicities were more frequent. Elderly unfit patients with comorbidities are candidates for palliative treatment such as R-Chlorambucil.

Two new agents were approved for the treatment of relapsed MCL, Bortezomib and Temsirolismus. Furthermore, Bendamustine and Lenalidomide demonstrated promising clinical activity. Allogenic stem cell transplantation was performed in selected cases of relapsed lymphomas, but large studies should be performed to define the role of stem cell transplantation in MCL management.

Because failure and relapses are inevitable, novel agents targeting pathways implicated in cell growth and survival regulation have been developed. One of those is the phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathway implicated in cell proliferation, grow and survival. Other research centered on targeting B-cell antigen receptor (BCR) signaling pathway. Bruton tyrosine-kinase (Btk) is required for BCR signaling and place an important role in B cell maturation and it is overexpressed in B-cell malignancies. Ibrutinib is a potent selected and oral inhibitor of Btk. An international, multicentric, phase 2 study of Btk inhibitor, Ibrutinib in relapsed or refractory MCL showed a 68% overall response rate.

Future clinical trials are needed for creating specific therapy targeting tumor biology markers and genetic abnormalities.