# session 10 – review lectures

## 108 GREY ZONE LYMPHOMAS

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**Introduction/Background:** Grey zone lymphomas were originally defined as lymphoid malignancies with certain shared features of classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL). These borderline tumors include nodular lymphocyte predominant HL (nLPHL), primary mediastinal large B-cell lymphoma (MLBCL), anaplastic large cell lymphoma (ALCL), and T-cell/histiocyte-rich B-cell lymphoma (T/HRBCL). With additional information regarding their unique morphological, immunophenotypical and molecular features, these entities are now more clearly defined.

**Results:** The transcriptional profiles and associated genetic signatures of specific grey zone lymphomas have led to the development of diagnostic immunohistochemical signatures and the identification of subtype- specific survival pathways and rational therapeutic targets. For example, the molecular signature of primary MLBCL shares important features with that of the clinically related disorder, cHL, including constitutive activation of NF-kB, near-uniform nuclear localization of the cREL NF-kB subunit and increased abundance of the NF-kB target, TRAF1. Morphologically and immunophenotypically defined T/HRBCLs resemble ''host response (HR)'' DLBCLs, which have a characteristic gene expression profile and increased numbers of CD2 and CD3+ tumor-infiltrating lymphocytes and interdigitating dendritic cells. Shared T/HRBCL and HR DLBCL clinical features include younger age at presentation, more frequent involvement of liver, spleen and bone marrow and less common genetic abnormalities (BCL2 or BCL6 translocations). More recently, the AP1- dependent overexpression of the immunoregulatory glycan-binding protein, galectin-1 (Gal1), was found to delineate cHL from the LBCL subtypes, MLBCL and DLBCL. Nodular LPHLs also lack Gal1 expression. However, ALCLs, which exhibit constitutive activation of AP1, concordantly express Gal1, cJUN and phospho-cJUN. Therefore, a functional signature of AP1-dependent Gal1 expression distinguishes cHL and ALCL from other grey zone lymphomas with shared morphologic and/or molecular features.

**Conclusions:** Specific grey zone lymphomas rely upon specific survival pathways associated with diagnostic immunohistochemical signatures.

## 109 CNS INVOLVEMENT IN LYMPHOMAS

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Secondary involvement of the central nervous system (CNS) by aggressive B-cell lymphomas is an infrequent but nearly always fatal complication. Although prophylactic treatment likely reduces the incidence of CNS relapse, it increases the toxicity of systemic chemotherapy and is unnecessary in most patients. This has led to the development of clinical risk paradigms to identify patients who might benefit from cerebrospinal fluid (CSF) prophylaxis, but even among these patients, only a minority ever develops disease. The risk of CNS spread appears to be particularly high among patients with extranodal diffuse large B-cell lymphoma and Burkitt lymphoma where it is a significant cause of treatment failure, and has led to the use of routine prophylaxis. Unfortunately, it is unclear if current prophylaxis is adequate. These findings indicate a need to develop and validate sensitive analytical methods for detection of occult CSF involvement to ensure optimal treatment, while reducing unnecessary prophylactic treatment. Regrettably, cytological examination of the CSF, the diagnostic ''gold standard'', has a low sensitivity and high false negative rate of up to 60%, but recent studies indicate that flow cytometry has a high sensitivity even with minimal disease burden. Therapeutically, evidence suggests rituximab may enhance the treatment efficacy. Thus, advances in early detection and treatment may significantly improve the outcome of leptomeningeal lymphoma.

## 110 CURRENT TREATMENT APPROACHES IN MULTIPLE MYELOMA

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Treatment of Multiple myeloma (MM) has remained stagnant for several decades; however, in the last few years major changes have emerged. In young patients the use of novel schemes based on Thalidomide, Lenalidomide, or Bortezomib appear to be superior to VAD as debulky pre-transplant regimens. Thus, with these novel drug combinations the majority of patients respond (>80% PR) with 10%-30% CR rate. These schemes do not affect stem cell collection, although some precautions should be taken with Lenalidomide. Interestingly, the initial CR rate obtained with thesecombinations (particularly with Bortezomib, as shown in two randomized trials) was upgraded following ASCT, which suggests that these novel treatments will not replace ASCT, but will help to enhance its activity, although the EFS and OS of this approach is still unknown. Regarding the role of novel drugs in maintenance therapy after transplant, two randomized trials have shown that Thalidomide maintenance prolongs EFS and OS, particularly in those patients who fail to achieve CR after Transplant. Nevertheless, prolonged treatment may be associated with more resistant relapses to salvage therapy. Accordingly, the current open question is the optimal duration of these treatments (maintenance vs consolidation). In elderly patients Melphalan-Prednisone (MP) has been the gold standard for over 40 years. However, recent data demonstrate that, in these patients the combination of any of the new agents (Thalidomide, Lenalidomide and Bortezomib) with MP is superior to the standard MP. An alternative to these MP combinations would be Lenalidomide+Dexamethasone, particularly using low dose Dexamethasone. One important goal in elderly patients will be to achieve the optimal balance between prolongation in survival and quality of life. The role of novel drugs in relapse MM is well defined, and in fact the overall survival prolongationobserved in myeloma patients is mainly due to the efficacy of Thalidomide, Lenalidomide and Bortezomib, in the relapse-refractory setting. Thalidomide represented the first step forward, and in combination with Cyclophosphamide and Dexamethasone is widely used in relapse MM. Single agent Bortezomib is significantly superior to Dexamethasone, and the efficacy increases upon combined with Anthracyclines or alkylating agents. Two randomized trials have shown that Lenalidomide+Dexamethasone is significantly better than Dexamethasone. Moreover, the activity may be enhanced by the combination of IMID's with Bortezomib. Overall, these data indicate that a new treatment sceneryhas emerged for MM patients.

## 111 CHRONIC LYMPHOCYTIC LEUKEMIA: PROGRESS AND CHALLENGES

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**Biology**: CLL is due to the accumulation of CD5+ B lymphocytes. Malignant cells express high levels of Bcl-2 anti-apoptotic proteins. Non-neoplastic stromal cells also play a key role in preventing apoptosis. B cell receptors of B CLL cells have highly selected IgVH gene usage, arguing in favor of a limited set of antigens triggering the disease. Around 40% of cases present unmutated IgVH genes and 60% mutated IgVH genes. ZAP-70 expression is associated with unmutated IgVH CLL. The most frequent cytogenetic abnormalities are del 13q and trisomy 12, whereas deletions of 11q, 17p and 6q are less frequent. The 13q14 regioninvolves a number of genes such as miR15a, miR16-1 and Leu2 whose downregulation increases the expression of BCL-2.

**Diagnosis**: The basic criterion is > 5,000 monoclonal B lymphocytes (SmIg (weak), CD5+, CD19+, CD20 (weak), and CD23+) in peripheral blood. Individuals with less than 5,000 lymphocytes *and* lymphadenopathy, splenomegaly, hepatomegaly or cytopenias due to bone marrow infiltration are considered to have Small Lymphocytic Lymphoma whereas those *without* these features are categorized as having Monoclonal B lymphocytosis (MBL).

**Prognosis**: Clinical stages and other simple parameters (e.g. doubling time) predict the course of the disease. Once patients require treatment, response predictors become very important since response to therapy determines survival. Abnormalities of 17p convey resistance to fludarabine and del(11q) poor and short responses. The power of IgVH mutations, ZAP-70 or CD38 expression to predict response has not been fully investigated.

**Treatment**: Modern therapy of CLL is based in chemo(immuno)therapy regimens which include purine analogs and monoclonal antibodies such as alemtuzumab or rituximab. With these regimens 80-90% of patients respond and the CR rate can be as high as 60-70%. Importantly in some of these responses no minimal residual disease can be detected, a situation which is associated with prolonged survival. Unfortunately all patients relapse. Because of this novel therapies aim at different targets including stromall cells. The prognosis of refractory cases is very poor. Allogeneic stem cell transplants with non-myeloablative regimens are increasingly performed in these cases.