session 10 – review lectures

108 GREY ZONE LYMPHOMAS
M.A. Shipp1
1Medical Oncology, Dana-Farber Cancer Institute, Boston, United States

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 (MBLCL), anaplastic large cell lymphoma (ALCL), and T-cell/histiocyte-rich B-cell lymphoma (THRLBL). 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 MBLCL shares important features with that of the clinically related disorder, cHL, including constitutive activation of NF-kB, near-uniform nuclear localization of the c-REL NF-kB subunit and increased abundance of the NF-kB target, TRAF1. Morphologically and immunophenotypically defined T/HRCLs 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/HRCLs 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 DLBCL subtypes, MBLCL 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
W.H. Wilson1
1Center for Cancer Research, National Cancer Institute, Bethesda, United States

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 is managed with prophylactic treatment. Despite the fact that CNS involvement is a significant cause of treatment failure, and has led to the use of routine prophylaxis, it is unclear if current prophylaxis is adequate. These findings indicate that the current open question is the optimal duration of these treatments (maintenance vs consolidation). In elderly patients, prophylactic treatment likely reduces the incidence of CNS relapse, it increases the CNS relapse rate, and it increases the toxicity of systemic chemotherapy and is unnecessary in most patients. This has led to the use of routine prophylaxis. 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 prophylaxis in survival and quality of life. The role of novel drugs in relapse MM is well defined, and in fact the overall survival prolongation observed 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 Dexamethasone and Cyclophosphamide widely in use in relapse MM. Single agent Bortezomib is significantly superior to Dexamethasone, and the efficacy increases even combined with Bortezomib. However, the activity may be enhanced by the combination of IMIDs with Bortezomib. Overall, these data indicate that a new treatment scenario has emerged for MM patients.

111 CHRONIC LYMPHOCYTIC LEUKEMIA: PROGRESS AND CHALLENGES
E. Montserrat1
1Department of Hematology, Institute of Hematology and Oncology, Barcelona, Spain

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 region involves a number of genes such as mir15a, mir16-1 and Len2 whose downregulation increases the expression of BCL-2.

Diagnosis: The basic criterion is > 5,000 mononuclear B lymphocytes (SmIg (weak), CD5+, CD19+, CD20 (weak), and CD23+). The diagnosis of CLL is based on clinical criteria (e.g. doubling time), morphology and 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 region involves a number of genes such as mir15a, mir16-1 and Len2 whose downregulation increases the expression of BCL-2.

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 carry 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 on 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 stromal cells. The progression of refractory cases is very poor. Allogeneic stem cell transplants with non-myeloablative regimens are increasingly performed in these cases.