Agressive Lymphoma – Pathology

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Gene expression profiling has defined major subtypes of aggressive non-Hodgkin's lymphomas (B-NHL) in recent years, in particular among diffuse large B-cell lymphomas (DLBCL). Specifically, a germinal center B-cell type (GCB DLBCL), an activated B-cell type (ABC DLBCL) and primary mediastinal B-cell lymphoma (PMBL) can be distinguished based on fundamental differences in underlying gene expression profiles. More recently, the Lymphoma and Leukemia Molecular Profiling Project (LLMPP)(Dave et al., NEJM 2006) as well as a major study conducted in Germany (Hummel et al., NEJM 2006) defined the highly aggressive entity of Burkitt lymphoma on a molecular level. Besides the molecular classification of B-NHL, gene expression signatures can also be used to predict clinical outcome. For example, the gene expression-based measurement of proliferation (proliferation signature) provides a powerful predictor of outcome in mantle cell lymphoma (MCL) that is superior to the immunohistochemical assessment of the Ki-67 index (Rosenwald et al., Cancer Cell 2003). How can these findings be translated into daily clinical practice?

Several attempts have been made to use a small set of immunohistochemical markers as surrogates for gene expression signatures. An example is the Hans-classifier (Hans et al., Blood 2004) that uses the immunohistochemical markers CD10, BCL6 and MUM1 to classify DLBCL into the GCB- and non-GCB subtypes. While this approach appears to be easily applicable in the daily routine, there are also limitations, and a considerable variation in the staining process (between different institutions) as well as in the scoring process (between different pathologists) have to be overcome. In particular, the germinal center-associated marker BCL6 appears to suffer from remarkable inter-laboratory variation (de Jong et al., JCO 2007).

Alternatively, quantitative RT-PCR (TaqMan) can be performed in routinely obtained formalin fixed and paraffin embedded tumor tissues. In mantle cell lymphoma (MCL), the quantitative mRNA expression measurement of 5 genes may be able to substitute for the proliferation signature determined by gene expression profiling (Hartmann et al., unpublished). Finally, the microarray platform itself may be used for diagnostic and prognostic purposes in clinical settings. Towards this goal, efforts are under way to achieve reliable and robust gene expression measurements across different laboratories. In one of these efforts, the Lymphoma and Leukemia Molecular Profiling Project (LLMPP) collaborates with Roche Diagnostics in the development of a diagnostic microarray. As a first step, a proficiency test between the 8 participating institutions was undertaken which showed highly consistent gene expression results of the same tumor tissues analyzed in a decentralized fashion.