inhibitor bortezomib has shown some activity in a recently completed phase II study of the IELSG (NCT00210327).
Aggressive anthracycline-containing regimens are not usually necessary and should be reserved for the few patients with high tumor burden and for those with diffuse large cell infiltration. These latter, indeed, should be treated according to the recommendations for diffuse large cell lymphoma.

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5
Primary mediastinal lymphoma

P.W.M. Johnson*. *Cancer Research UK Centre, Southampton, United Kingdom*

Primary mediastinal B-cell lymphoma is now recognised as a discrete clinico-pathologic entity. Molecular analysis reveals it to be different from other types of large B-cell lymphoma, particularly in the activation of the NF-kB pathway and expression of nuclear transcription factors. Retrospective analysis of large series suggests that it may respond better to multi-agent dose-dense chemotherapy regimens than to the more commonly-used CHOP, although this has not been examined prospectively. The addition of Rituximab may mitigate such differences, and may also diminish the role of consolidation radiotherapy, which is widely used to treat residual mediastinal masses. FDG-PET scanning is increasingly used in the management of lymphoma for the evaluation of residual masses after initial therapy, although there are important questions about specificity, particularly in large B-cell lymphoma following treatment with Rituximab, where the false positive rate appears to be relatively high. This is a particularly relevant issue for PMBL, and requires prospective examination, in the hope that this may allow the de-escalation of treatment if it can be shown to yield reliable prognostic information. The relative rarity of this type of lymphoma necessitates international collaboration in clinical trials, with the prospective clinico-pathologic study, IELSG 26 already underway.

6
Molecular pathology of B cell lymphoma

R. Dalla-Favera*. *Columbia University, Department of Pathology and Genetics, New York, USA*

B-cell derived Non-Hodgkin Lymphoma (B-NHL) represent a heterogeneous group of malignancies among which diffuse large cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and Burkitt lymphoma (BL) represent common entities for which some understanding of their pathogenesis has been acquired. With the exception of MCL, all B-NHL arise by malignant transformation of B cells within the germinal center (GC), the structure where antigen-stimulated B cells undergo rapid proliferation and

specific genome remodeling processes such as Immunoglobulin (Ig) somatic hypermutation (SHM), and class switch recombination (CSR), allowing the expansion and selection of B cells with high affinity for the antigen and their further differentiation into memory B cells and plasma cells [1].

1. Two mechanisms of genetic lesion in B-NHL. The pathogenesis of B-NHL is associated with errors in genetic functions specific to GC B cells: (i) chromosomal translocations that lead to deregulated expression of oncogenes (BCL2, BCL6, c-MYC) and are thought to derive from DNA breaks associated with the Ig remodeling mechanisms (VDJ recombination, SHM, and CSR); and (ii) aberrant somatic hypermutation (ASHM), which is active in the majority of diffuse large B cell lymphomas (DLBCL) causes mutations in the 5′ region of multiple oncogenes and is due to the misfiring of SHM on non-physiologic targets. The role of CSR and SHM in lymphomagenesis was demonstrated in mice by crossing three oncogene-driven mouse models of B-NHL with mice lacking activation-induced cytidine deaminase (AID), the enzyme required for both processes. The results showed that AID deficiency prevents the development of GC-derived B-NHL, indicating that AID is required for GC-derived lymphomagenesis [2].

2. BCL6, the master regulator of GC development. The unique biology of GC and its implications in the pathogenesis of GC-derived B-NHL is explained in part by the function of the BCL6 gene, which encodes a transcriptional repressor necessary for GC formation and which is also a common pathogenetic target of both translocations and SHM. Recent results [3–4] have shown that in the first phase of GC development (centroblasts), BCL6 is involved in the repression of a number of biological functions including: (a) the response to DNA damage: (b) cell cycle arrest; (c) T-cell- and cytokine-mediated activation; (d) antiapoptotic pathways; (e) genomic instability and replication stress; (f) plasmacell differentiation. In a second phase of GC development, BCL6 is downregulated, thus allowing GC centrocytes to reestablish the above functions, including the ability to arrest proliferation and differentiate into plasmacells.

3. Genetic lesions deregulate the BCL6 program in B-NHL. The elucidation of the multiple BCL6 functions has allowed the development of a unifying model for the pathogenesis of major B-NHL types. In fact, the different NHL-associated chromosomal translocations as well as other B-NHL-associated genetic lesions appear to disrupt pathway that are regulated by or regulate BCL6: (1) chromosomal translocations involving the c-MYC gene prevent its downregulation by BCL6 in BL, and a fraction of DLBCL; (2) chromosomal translocations involving the BCL2 gene prevent downregulation by BCL2 in FL, and a fraction of DLBCL; (3) the pathway leading to BCL6 downregulation and BLIMP1 activation is disrupted by chromosomal translocations and mutations affecting BCL6 or by inactivation of BLIMP1 in non-overlapping cases of DLBCL [1]; both these lesions are often associated with genetic lesions leading to the constitutive activation of the NF-kB transcription complex in the majority of DLBCL, thus providing an anti-apoptotic stimulus in this disease [5]. The discovery of these genetic lesions and their conceptual organization in defined biological pathways has important implications for the definition of additional B-NHL subtypes and their specific therapeutic targeting.

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Leukaemias

7
Is molecular biology something more than occupational therapy for basic scientists?

M.F. Fey*. *University Hospital and Inselspital, Department of Medical Oncology, Bern, Switzerland*

Our understanding of the molecular pathology of many haematological neoplasms has grown considerably over the last few decades, and years. Whilst such a gain of information is undeniably fascinating, the clinical relevance of molecular data needs to be reviewed critically.

Diagnosis of leukaemias and lymphomas still rests on morphology, topped up with immunological markers (used either in flow cytometry, or as histological markers). However, the advent of molecular markers has enabled us to pinpoint particular leukaemias or lymphomas as “entities” that were previously not recognised as such. NPM+ acute myeloblastic leukaemias are a point in case. NPM+ AML occurs more often in women than men, has high platelet counts at diagnosis, high remission rates and a reasonably good prognosis even without allogeneic stem cell transplantation.

Many molecular markers are prognostic, indicating either a good natural history of the disease (for example, CLL with del13q detected by FISH), or a bad one (for example, NOTCH1 mutations in adult T-cell ALL). In many instances, however, clinical risk scores are still more important than the molecular factors. For example, commonly used risk scores used in B-cell lymphoma (IPI and FLIPI) are based on simple clinical and routine lab criteria, and do not incorporate any molecular data.

A common misconception has it, that prognostic markers guide treatment choice, where intuitively patients with a “terrible” prognosis are offered more aggressive therapy than those with a better outlook. However, a predictive marker should help to identify patients who will respond well to a given therapy, and sort out patients with an *a priori* low chance of benefiting from a specific compound or treatment modality. Some practical examples show the way to go. The BCR-ABL + leukaemias will respond to blockade of this fusion molecule, and AML with duplications of the FLT3 gene may possibly respond to FLT3 inhibitors, regardless of whether they imply a good or a bad prognosis. In many neoplasms, however, there are still no specific drugs targeting given molecular abnormalities. For example, there is no compound in clinical use for the specific therapy of NMPmut AML. Likewise, the practical clinical relevance of molecular profiles of leukaemias or lymphomas worked out by microarrays still