



Conquering Blood Diseases –
From Research to Patient Care

Special Problems in B-Cell Lymphoma: An Historical Perspective

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50 years ago (1958)

The Rappaport Classification system for lymphomas had recently been introduced (1957). In that scheme, lymphomas were considered either nodular or diffuse and either well differentiated, poorly differentiated, undifferentiated, or mixed. The term histiocytic was introduced based upon the belief that neoplasms of large cells were derived from non-lymphoid cells. It is likely that a case of primary mediastinal lymphoma would have been called “diffuse histiocytic lymphoma,” a case of marginal zone lymphoma called “diffuse well-differentiated lymphoma,” and a case of Burkitt lymphoma (which had just been described in 1957) called “diffuse undifferentiated lymphoma.” Available treatments in 1958 included a few alkylating agents (nitrogen mustard), anti-metabolites (methotrexate), and external beam radiotherapy. Treatment was largely palliative.

25 years ago (1983)

The Working Formulation (WF) was published in 1982, although getting there had not been easy. Prior to 1982, several classification systems were in use throughout the world, none of which was universally accepted. It was only after reviewing over 1000 cases with corresponding clinical data and several years of meetings that the WF came about. It distinguished lymphomas based largely on the clinical course (low grade, intermediate grade, and high grade) and these three groupings were then subdivided into classes based upon morphologic features. In this system, many cases of primary mediastinal lymphoma would likely have been called WF category G (intermediate grade – diffuse mixed with sclerosis), Burkitt lymphoma called WF category J (high grade – small, non-cleaved), and most cases of marginal zone lymphoma called WF category A (low grade – small lymphocytic). In 1983, Isaacson and Wright first described MALT lymphoma as a unique entity. In the therapeutic arena, patients could now be cured with some reasonable frequency thanks to combination chemotherapy. The so-called third generation regimens were in their heyday, and 1983 saw the publication of the M-BACOD regimen, which suggested superiority over CHOP chemotherapy. Of course, M-BACOD along with the other third-generation regimens was later proven to be simply equivalent to CHOP.

Present day

The WHO classification system is in use and represents 50 years of refinement over previous systems. Whereas the Working Formulation included 10 distinct entities, the WHO classification has over 40. Similar to the effort required to create the WF, the new system represents a major effort over many years involving hematopathologists and clinicians from throughout the world. We now have a platform that recognizes lymphomas as distinct biologic entities with unique clinical courses. It has also created the opportunity for meaningful translational research, such as gene expression profiling, which has taught us that primary mediastinal lymphomas are a biologically distinct subtype and Burkitt lymphomas can be more reliably be identified by their molecular signature. The improved classification, by clearly delineating disease entities, has also facilitated the interpretation of clinical research. Finally, in 2008, we are now squarely in the era of targeted agents. For B-cell lymphomas, rituximab ushered in this era with a bang and now we earnestly search for the next breakthrough discovery that will move the field forward in a way that makes a difference for patients.

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