Introduction to a Clinical Review Series on Aggressive B-Cell Lymphoma

Laurie H. Sehn
Department of Medical Oncology
British Columbia Cancer Agency
Vancouver, BC Canada

The term “aggressive lymphoma” has been historically applied to highly proliferative lymphomas that clinically evolve over weeks to months and usually require immediate intervention. Similar to the descriptive terms coined by the Working Formulation Classification in the 1980’s, which categorized lymphomas as indolent, intermediate grade and high grade, aggressive lymphomas have been defined by clinical behavior and were frequently grouped within the context of clinical trials such that collective treatment strategies could be evaluated. In fact, some of the most influential trials guiding lymphoma management have broadly included patients with aggressive lymphoma, such as the Intergroup trial comparing CHOP with third generation anthracycline-based regimens and the Parma study of autologous stem cell transplantation for relapsed disease. Over the last several decades, improved biologic insight has lead to a refinement in lymphoma classification such that unique clinico-pathologic entities are now distinguished. Recent developments have further unveiled the complexity of lymphomas with the recognition of unique molecular subtypes and a growing list of genetic aberrations that are variably present. The paradigm of management has shifted from grouping lymphomas based on like-behavior to segregation, with the goal of individually tailoring therapy based on underlying molecular mechanisms. The articles within this series will review progress made within the most commonly encountered aggressive B-cell lymphomas, with the aim of highlighting how a better understanding of the underlying disease mechanisms is translating into more rational and effective therapeutic strategies.

The reviews in this series include the following:

- Kieron Dunleavy and Wyndham H. Wilson: “Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma-Do they require a unique therapeutic approach?”

DLBCL is the most common aggressive B-cell lymphoma, however, it has become clear that it should no longer be considered a singular entity. The World Health Organization (WHO) Classification of lymphoid malignancies now recognizes a sizable list of clinical and biologic subtypes within large B-cell lymphoma. Gene
expression profiling studies have identified at least 2 molecular subtypes, called germinal center B-cell (GCB) and activated B-cell (ABC) which represent lymphomas arising from different stages of B-cell differentiation. Most importantly, the molecular subtypes of DLBCL are driven by very distinct oncogenic mechanisms and may selectively benefit from novel approaches. Improved outcome with the addition of rituximab in patients with DLBCL was first reported fifteen years ago and since that time R-CHOP has remained the standard of care. However, potential therapeutic targets have recently been identified and lead to the development of a multitude of promising agents that are undergoing investigation. Further progress in DLBCL will require that clinical trials recognize its molecular diversity and selectively enrich for patients who are most likely to benefit from alternate strategies.

While morphologically resembling DLBCL, PMBCL was initially described as a separate clinical subtype of DLBCL as patients were typically younger, more likely to be female and presented with disease primarily involving the mediastinum. In the last version of the WHO Classification of lymphoid malignancies, PMBCL was officially recognized as a unique entity based on the identification of a characteristic gene expression signature, separate from GCB and ABC subtypes, but exhibiting overlap with Hodgkin lymphoma. Patients with PMBCL have been typically incorporated within clinical trials of DLBCL, although they have constituted a minority of patients resulting in limited power for subgroup analysis. Outcome curves demonstrate a unique profile whereby relapses beyond two years are infrequent. While similar treatment strategies for PMBCL and DLBCL have been employed, studies suggesting benefit with alternate approaches such as DA-EPOCH-R highlight the need to investigate PMBCL separately. Recently, genetic aberrations that are differentially observed in PMBCL have been identified, including dysregulation of janus kinase 2 (JAK2) and programmed death ligands (PDL) 1 and 2. Novel agents that may selectively benefit PMBCL are being explored. The recent recognition of mediastinal grey zone lymphomas with clinical and pathologic features intermediate between PMBCL and classical Hodgkin lymphoma present an additional diagnostic and therapeutic challenge.

Transformation from an underlying indolent lymphoma to an aggressive behaving lymphoma most typically results in a lymphoma morphologically resembling de novo DLBCL. However, the pathogenic mechanisms that underlie the evolution of an indolent lymphoma to an aggressive lymphoma are gradually being elucidated and demonstrate wide biological diversity. The complexity is further compounded by the recognition that indolent lymphomas are composed of numerous sub-populations of tumour cells with distinct oncogenic drivers, and therefore establishing the key events that transform behaviour is often difficult. Nonetheless, transformation has a major impact on the natural history of indolent lymphoma, significantly decreasing survival. Management of transformed lymphoma is complicated by patient heterogeneity, including variable indolent histologic subtypes and prior exposure to chemotherapeutic agents. Unfortunately, these patients are routinely excluded from clinical trials, and therefore the majority
of studies that guide management have been retrospective. Recent reports suggest that outcomes have improved since the availability of rituximab and therefore a reconsideration of current practice is warranted.

Based on the presence of the pathognomonic t(11,14) translocation and the resultant overexpression of cyclin D1, MCL is readily distinguishable from other aggressive B-cell lymphomas. Research efforts have further delineated the role of additionally acquired genetic alterations in directing its diverse pathogenesis and heterogeneous behaviour. Based on its relatively low incidence, collaborative efforts have been necessary to evaluate therapeutic strategies in MCL and represent an exemplary model for other areas of lymphoma research as patient populations get further refined. Despite the routine application of intensive therapeutic strategies, MCL remains incurable. The development of novel agents targeting key components of cell cycle regulatory pathways, such as the B-cell receptor pathway, have shown particular promise in the treatment of MCL and have called into question current management algorithms.

Despite their differences, the challenges in making further progress in aggressive B-cell malignancies will be shared. The biological diversity, both between and within the histological subtypes must be recognized in order for individualized management strategies to be evaluated. This will require the availability of standardized molecular tests for the purpose of accurate diagnosis, improved prognostication and biomarkers with predictive capacity to allow for selective use of novel targeted therapies. As outcomes continue to improve, larger patient trials will be necessary to demonstrate further incremental benefit, while further segregation of patients into defined molecular categories will limit the numbers of patients appropriate for individual trials. The logistics of performing biomarker-driven trials will add complexity to trial design and the necessity to perform specialized tests centrally will limit the numbers of patients eligible for inclusion and delay treatment initiation. In light of limited resources and patients available for trial participation, candidate drugs will need to be prioritized based on sound preclinical and early clinical studies with attempt to identify those affecting key driver pathways. Importantly, wider collaborative efforts will be necessary to allow efficient evaluation of the large number of exciting agents in development to ensure overall success.
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