The diversity challenges in follicular lymphoma

Follicular lymphoma (FL) is the prototypical indolent B-cell lymphoma and characterized by a diverse range of clinical presentations that occur at virtually any age and involve nearly any organ. The spectrum of clinical behavior in FL ranges from spontaneous regressions to histologic transformation and is largely unpredictable at the time of diagnosis. The underlying biologic basis for this broad range of clinical behavior is not completely understood, but clearly involves a dynamic interplay between intrinsic factors including tumor genetics, extrinsic factors such as interactions with the surrounding tumor microenvironment, and the integrity of host immunosurveillance. Further, these interactions perpetually evolve within each patient often under the selection pressure of multiple therapies. The long natural history of FL coupled with its clinical diversity creates fundamental challenges in developing personalized management strategies for FL patients since "one size fits all" approaches are imprudent. Beyond clinical management, the biologic diversity across the FL spectrum creates challenges for identifying the key genetic or epigenetic events that drive disease progression as these factors also evolve over decades.

Despite these challenges, the general outlook for most FL patients is improving coincident with a more nuanced understanding of underlying disease biology, more precise diagnostic and monitoring tools, and a sharp increase in novel treatments including both targeted pathway inhibitors and immunotherapy approaches. Indeed, the overall survival across the disease spectrum of FL continues to improve with each decade (1). It is equally important to emphasize the current clinical and research hurdles related to the diversity of FL. Patients who relapse quickly after frontline therapy clearly have the worst clinical outcomes, but we currently lack the tools to precisely identify these patients at the time of diagnosis (2). Multiple therapeutic options now exist for patients and new treatments continue to emerge, but we have very few predictive biomarkers that guide the selection of agents. We have only a limited concept of how to factor in the diversity of the patients themselves as it relates to their age, sex, race, or ethnicity to treatment choices. Do all subgroups respond the same to individual treatments or are there important differences across subgroups? Lastly, it is of serious concern that most novel treatments are prohibitively expensive or require a level of access to health care that only applies to a limited group of patients. Unless these disparities are addressed, then FL patients who are uninsured or underinsured as well as those who lack a sophisticated ability to navigate complicated medical systems are unlikely to benefit from new treatments, regardless of their efficacy.

The following special series of *Annals of Lymphoma* was constructed to highlight our current understanding of the molecular biology that underpins this clinical diversity in FL as well as to provide an update on the rapidly changing treatment landscape in both the frontline and relapsed settings. This special series features prominent lymphoma researchers who provide detailed presentations of the current understanding of FL pathobiology, diagnostic and prognostic tools, and management approaches. The ultimate goal is to identify and target the relevant molecular pathways/mutations that can be applied to individual patients leading to precision treatment of FL (3). It is likely that therapeutic breakthroughs will result from an improved understanding of the critical drivers that characterize FL subsets, rather than the empiric use of agents or combinations.

Zhou, Pittaluga and Jaffe first discuss the multi-stage development of conventional t(14;18)-positive FL from FL-like B cells to pre-malignant lesions and finally to full blown malignancy with nodal involvement. They also highlight FL variants including t(14;18)-negative FL that is genetically more heterogenous with pathogenic mechanisms that are less well understood. They remind us to consider the diversity of FL as a group of B-cell neoplasms with important distinctions despite overlapping features. Duodenal-type FL, pediatric-type FL, testicular FL, and primary cutaneous follicle center lymphoma are discussed with an emphasis on the features that distinguish them from conventional FL. Recognition of these entities is critical as they are often diagnostic dilemmas and may require specialized management.

Perrett and Okosun provide a comprehensive overview of the current landscape of genetic and epigenetic alterations found in FL based on landmark high throughput sequencing studies. They highlight that both B-cell lymphoma-2 (BCL2) translocation and mutations in chromatin-modifying enzymes are considered hallmark genetic events responsible for the initiation and/or maintenance of FL and discuss recently appreciated secondary genetic mechanisms associated with oncogenic signaling, cell cycle regulation, and altered immune surveillance. The spatial and temporal heterogeneity of FL

is emphasized including clonal evolution and changes in genetic features over the course of illness and the methods for best studying this clonal evolution are discussed.

Nath, Tang and Gandhi detail our current understanding of the central role of the tumor microenvironment in FL and its impact on disease behavior. Highlighting the composition and architecture of the non-malignant immune cells seen in FL lymph nodes, they describe how the FL microenvironment is distinct from other B-cell lymphomas and how genetic aberrations in tumor cells serve to 're-educate' surrounding infiltrating cells and establish dependence for proliferation and survival. Specific cells and their role in both immune effector responses and immune evasion are discussed. They also discuss the complex interplay between immune cells with non-cellular components including the cytokine and chemokine milieu. Finally, the role of the microenvironment for risk-stratification and the development of novel therapeutics is discussed.

Liu, Silva, and Kridel discuss our current ability to identify 'high-risk' subsets of FL that progress shortly after frontline therapy including the current limitations at establishing a definitive biologic basis for these subsets. They discuss the strengths and weaknesses of various risk stratification tools including clinical prognostic indices, clinico-genetic indices, functional imaging studies results after therapy, individual gene mutations, gene expression profiles, and emerging tools for measuring residual disease at the molecular level. After comprehensively outlining the current state of the science in risk-stratification of FL, they lay out a blueprint for addressing this unmet need as a backbone for potential precision medicine strategies.

On the heels of these biologic-based essays, the series shifts toward a discussion of clinical management within the context of novel biologic insights. Luminari and Tarantino discuss the current treatment approach to newly diagnosed FL with consideration of age and pre-treatment prognostic subgroups. The authors outline the pros and cons of various frontline treatment approaches emphasizing the need to balance the possibility of durable remission with expected toxicities and its impact on quality of life. Focusing on common clinical questions, they provide a balanced discussion outlining the key aspects of making these important management decisions.

Rodgers and Barr provide a comprehensive summary of the key aspects of making treatment decisions for patients who require second line therapy, including those with disease that has relapsed shortly after frontline therapy. Through illustrative and common scenarios, the authors highlight the treatment choices for each scenario and frame the discussion based on the most relevant factors to consider for these decisions. The authors conclude by discussing emerging treatments and how these are likely to impact the treatment choices for relapsed FL in the future.

Pott, Wellnitz and Ladetto address the current understanding of the role of testing for minimal residual disease (MRD) in FL including technical issues related to limit of detection, tissue source, and various methods. In this rapidly developing field, they highlight the potential to use MRD kinetics or landmark analyses after treatment to guide individualized treatment or as an endpoint for clinical trials testing novel treatment. Finally, they discuss combining information from MRD with functional imaging to refine the depth of response in FL.

Batlevi and Morschhauer tackle the challenge of illustrating the rapidly expanding field of novel targeted agents that are currently in development. They discuss multiple agents including those targeting Bruton tyrosine kinase, BCL2 mimetics, and phosphatidylinositol 3-kinase (PI3K) pathway inhibitors. Further, they discuss the role of lenalidomide for the treatment of both untreated and relapsed FL along with the newly available inhibitor of enhancer of zeste homologue 2 (EZH2) which provides use with the first example of precision medicine in FL. They conclude by describing many exciting combinations of agents which may provide even durable remissions without the need for continuous dosing.

In the final chapter, Khurana and Ansell discuss myriad immunologic agents and immunology approaches including chimeric antigen receptor (CAR) T-cell therapies that are current being investigated in FL. From monoclonal antibodies to antibody-drug conjugates, they describe various agents that target surface receptors in FL and describe the unique mechanism of action for bispecific monoclonal antibodies as well as immune checkpoint inhibitors that target both the adaptive and the innate immune system. They also conclude with a comprehensive list of combinations that include immunotherapy agents that are current in development.

The collection of manuscripts found in this special series of *Annals of Lymphoma* eloquently highlights some of the current challenges in approaching patients with FL; for example, what are current ways to determine prognosis given biologic heterogeneity? How can we use molecular monitoring to understand disease burden at the time of diagnosis and throughout

a patient's disease course to stratify risk over time? How can we use currently available knowledge on clinical and molecular markers to guide therapy? The increasing complexity of FL begs for greater insight into how best to integrate this wealth of knowledge into the daily care of patients. This catalogue of cutting-edge information supplies clinicians and scientists with a comprehensive resource to integrate this knowledge and apply it to the care of patients. We envision this special series of *Annals of Lymphoma* to be essential reading for clinicians and scientists seeking to understand biologic aspects of FL, nascent discoveries driving FL pathogenesis, and highlights of key factors that influence prognosis and identification of patients with high-risk disease. We sincerely hope that the amalgamation of this vast repertoire of knowledge can facilitate precision care and helps us more towards a refined approach to the care of patients with FL.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Lymphoma* for the series "Follicular Lymphoma". The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (https://aol.amegroups.com/article/view/10.21037/aol-2022-1/coif). The series "Follicular Lymphoma" was commissioned by the editorial office without any funding or sponsorship. MR served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Annals of Lymphoma* from October 2020 to September 2022. CC served as the unpaid Guest Editor of the series, and reports research funding from Gilead, Genetech, BMS and Verastem. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. Blood 2013;122:981-7.
2. Mir F, Mattiello F, Grigg A, et al. Follicular Lymphoma Evaluation Index (FLEX): A new clinical prognostic model that is superior to existing risk scores for predicting progression-free survival and early treatment failure after frontline immunochemotherapy. Am J Hematol 2020;95:1503-10.
3. Sorigue M, Cañamero E, Sancho JM. Precision medicine in follicular lymphoma: Focus on predictive biomarkers. Hematol Oncol 2020;38:625-39.

Mark Roschewski

Carla Casulo

Mark Roschewski, MD
Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.
(*Email: mark.roschewski@nih.gov*)
Carla Casulo, MD
Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA.
(*Email: carla_casulo@urmc.rochester.edu*)
Received: 17 February 2022; Accepted: 02 April 2022; Published: 30 June 2022.
doi: 10.21037/aol-2022-1
View this article at: https://dx.doi.org/10.21037/aol-2022-1

doi: 10.21037/aol-2022-1
Cite this article as: Roschewski M, Casulo C. The diversity challenges in follicular lymphoma. Ann Lymphoma 2022;6:4.