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CLINICAL TRIALS AND OBSERVATIONS

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The rise of a new "great teacher"

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In this issue of *Blood*, Advani and colleagues[1] from the T-cell Project provide an overview of the largest cohort of patients with angioimmunoblastic T-cell lymphoma (AITL) reported to date. They found that outcomes remain disappointing, despite the introduction of novel agents, and confirm that only a very small minority of patients receive consolidation with autologous stem cell transplantation (ASCT). They also propose a new AITL prognostic score.

Approximately 10 years ago, Joe Connors[2] aptly identified Hodgkin lymphoma (HL) as the "great teacher" in oncology. That venerable title was bestowed on the ground that generations of oncology trainees learned their clinical research lesson by pouring over dozens of randomized trials in HL, a neoplasm no less rare than peripheral T-cell lymphomas (PTCLs). Are there any lessons that current and future generations of trainees can learn from PTCL? Is AITL the great teacher of the next generation of hematologists/oncologists?

Our understanding of AITL has evolved over the past 40 years from a puzzling and obscure lymphoproliferative disorder to a well-defined (if protean) aggressive neoplasm with highly characteristic clinical features, histology, immunophenotype, gene expression, and mutational signatures.[3] Along the way, AITL has provided endless learning opportunities for perceptive students, leading to landmark observations, hypotheses, and studies that have changed the field of T-cell lymphoma. Even more importantly, these observations have built the architecture of an interpretive framework that sheds light on many of the puzzling manifestations of this T-cell neoplasm.

Lesson 1 is the recognition that tumor cells in AITL have significant molecular overlap with normal T follicular helper (TFH) cells,[4] pivotal regulators of B-cell differentiation in the germinal center, provided the conceptual background to begin understanding the dysregulated B-cell activation that is so characteristic of AITL.[3] Hypergammaglobulinemia, autoimmunity, excessive production of cytokines (interleukin-6 [IL-6], IL-10, and IL-21), expansion of B-cell immunoblasts and plasma cells (sometimes to a degree to suggest plasma cell leukemia),[5] and reactivation of the Epstein-Barr virus (EBV) are the hallmarks of AITL.[3] The objective responses observed in patients with relapsed and refractory AITL with calcineurin inhibitors, such as cyclosporine,[6] likely reflect the TFH-like biology of AITL. Finally, the recognition that subsets of PTCLs also express TFH markers, often with overlapping clinical features, led to the creation of a new World Health Organization lymphoma category named "AITL and other nodal T-cell lymphomas of TFH origin."[3]

Lesson 2 is that variable but sizeable fractions of patients with AITL harbor distinct loss-of-function or neomorphic mutations for genes encoding epigenetic regulators, such as TET2 (~80%), IDH2 (20% to 40%), and DNMT3A (20% to 38%), or for small GTPases, such as RHOA (~70%).[7] Thus, AITL has been proposed as the model of epigenetically driven lymphoma. As if on cue, when some of these mutated genes (TET2 and RHOA) are expressed in mice, or when the wild-type genes are knocked out, the animals develop mature T-cell lymphomas with a TFH phenotype, resembling AITL.[7] Intriguingly, some of the same mutations (TET2 and DNMT3A) that are the hallmark of clonal hematopoiesis and are frequently found in myeloid neoplasms, can also be detected in normal-appearing bone marrow progenitor cells and tumor-infiltrating cells from patients with AITL, revealing a previously unknown link between myeloid hematopoiesis and T-cell neoplasms.[7] The presence of these mutations, and the new insight of the genetic link between AITL and myeloid neoplasms, prompted the study of hypomethylating agents in AITL.[8] Likewise, studies of epigenetic drugs, such as the histone deacetylase (HDAC) inhibitors, suggest greater efficacy in AITL than other PTCLs.[9]

Lesson 3 is that AITL and other TFH cell lymphomas being infrequent neoplasms, international prospective collaborations are essential to accrue the large datasets needed to draw confident conclusions about prognostic factors and outcomes. The study by Advani and colleagues reveals that AITL may be the most common type of PTCL worldwide (PTCL not otherwise specified being a wastebasket category), a finding supported by another study.[10] Advani and colleagues[1] show that the outcome of patients with AITL treated with anthracycline-based regimens has not improved over the study period (2006-2018) and remains disappointing (44% 5-year overall survival [OS]).[1] It also shows that despite evidence suggesting a benefit for ASCT in first complete remission, nearly 90% of the patients did not receive it.[1]

The study identifies POD24 as a powerful discriminator of 2 subgroups with vastly

different survival outcomes. It also presents a new prognostic AITL score that includes inflammatory biomarkers (β2 microglobulin [β2M] and C-reactive protein [CRP]) and shows greater discriminant power compared with other prognostic indices. Considering that β2M and CRP are routine tests, the new score has potential for wide application, if prospectively confirmed. The minimal outcome difference predicted between low and intermediate risk groups (<10% for both OS and progression-free survival [PFS]),[1] however, suggests limited clinical utility to the distinctions between these 2 risk groups. The impact of plasma EBV DNA in this cohort would have been of interest, but that data were inconsistently obtained.

Since this study is the first analysis of a large cohort of patients with AITL spanning the pre- and post-HDAC inhibitor era, the impact of this variable on outcomes is of great interest. It is surprising that the study found no OS or PFS differences, given multiple findings of durable responses with these drugs in AITL. As the number of patients treated with HDAC inhibitors in the 2 groups is not reported, it is possible that small differences may have been missed.

In summary, the study of AITL has already produced many discoveries, spanning genetics, immunology, and preclinical models, identifying a unique family of lymphomas and a valuable model to study epigenetic therapy. One wonders if Frizzera and colleagues had any idea of what they were kicking in motion when they published their initial observations on "a new disease with a lymphoma-like clinical presentation" in 1974.[11] Whether they did or not, we owe them. Hematologists/oncologists, no less than everyone else, like a good story when it comes around. And everyone loves a great teacher.

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HEMATOPOIESIS AND STEM CELLS

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Unwinding the role of Chd8 helicase in hematopoiesis

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In this issue of *Blood*, Tu et al report an essential role for the autism-associated Chd8 chromatin-remodeler in the survival and genome integrity of hematopoietic stem and progenitor cells (HSPCs), through interactions with P53 and the ataxia telangiectasia mutated (ATM) protein kinase.[1]

Maintenance of blood cell homeostasis requires highly orchestrated changes in patterns of gene expression in stem cells and progenitors differentiating throughout the hematopoietic hierarchy. Chromatin remodeling complexes play an essential role in regulating DNA accessibility for transcription factors, other epigenetic modifiers, and the DNA repair machinery. Variations in the subunit composition of these complexes allow the coordinated expression of a large number of genes in a timely and cell-specific manner. Chromodomain helicase DNA-binding (Chd) proteins constitute a subtype of chromatin remodeling factors, which use ATP to change chromatin structure.[2] Nine different Chd helicases (Chd1 to 9) have been described in vertebrates, and several studies in the last few years have unraveled their role in hematopoiesis. Of note, Chd2, 4, and 7 have been previously shown to regulate lineage differentiation, cell survival, and maintenance of genome integrity, thorough interaction with a plethora of partners, such as Runx, Ets, and Gata factors.[3-5] Importantly, deficiency of CHD4 or CHD7 was shown to increase sensitization of acute myelogenous leukemia blasts to genotoxic stress and to delay leukemogenesis, respectively, making CHD helicases an attractive target for therapeutic interventions against leukemia.[6,7] Now, Tu et al implicate a new Chd helicase (Chd8) in hematopoiesis and in the maintenance of HSPCs.

Using the Mx-Cre inducible system, Tu et al show that CHD8 deficiency results in acute pan-cytopenia and bone marrow failure in mice. Analysis of the HSPC compartment 6 days after induction of Chd8 deficiency with poly(I:C) revealed impaired stem cells reconstitution potential and a drastic