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T-cell lymphomas: A 5-body problem

The 2 adjectives most commonly used to describe T-cell lymphomas (TCLs) are “rare” and “heterogeneous” which, without qualifiers, grossly understates the rarity and heterogeneity of these lymphoproliferative disorders. Per the Orphan Drug Act of 1983 [1], any disease which occurs in fewer than 200,000 Americans is considered rare. Mature T and NK-cell malignancies meet this definition even when viewed as a monolithic entity. That makes each individual diagnosis of the 29 listed in the World Health Organization’s categorization the rare of the rare [2]. Importantly, the differences between the 29 are not small: the spectrum goes from lymphomatoid papulosis—a generally indolent CD30-positive skin disorder with a 5-year overall survival (OS) approaching 100% [3]—to acute subtype adult T-cell leukemia/lymphoma (ATLL)—an aggressive T-cell proliferation involving all compartments of the body with a median OS of 8 months (Fig. 1) [4]. It is unsurprising then that developing effective treatments for TCLs has been more challenging than for their more common B-cell counterparts.

Biology of T lymphocytes adds to the challenge, as they have a complex developmental pattern that is both stochastic and dependent on the microenvironment [5]. Even after nominal maturation, T cells maintain significant plasticity. It is by no means certain, then, that the immunophenotype of a TCL implies its cell of origin. In fact, it is clear from transgenic mouse models that at least one subtype, angioimmunoblastic T-cell lymphoma (AITL), characterized by a T follicular helper cell phenotype and reviewed in this issue by Ma and colleagues [6], may develop from any CD4-positive T cell that gains TET2 and RHOA mutations. Similarly, 2 key proteins of the Human T-Lymphotropic Virus-1 (HTLV-1), HTLV-1 bZIP factor (HBZ) and Tax, may drive any infected T cell to a T-regulatory (Treg) phenotype characteristic of ATLL [7], the management on which is reviewed here by Ishitsuka [8]. A small population of malignant T-cell precursors comes close to the stem cell theory of cancer and may explain both the ever-shifting phenotypes of some TCLs and their resistance to treatment.

Regardless of its origin, the characteristic immunophenotype of each TCL subtype points to another fact of T-cell biology, one that may be the biggest hurdle to rational development of new treatments: T lymphocytes are promiscuous in their interactions both among themselves and with many other components of the tumor microenvironment (TME) [9]. As physicists and readers of Chinese science fiction know, there is no general solution for interactions between 3 mutually dependent bodies in motion, and the resulting system is chaotic in the mathematical sense. A hypothetical 5-body problem of TCL-TME interactions (Fig. 2) and the perturbations of the system caused by our therapeutic interventions is likely to be as chaotic. Any predictions or post-hoc explanations of clinical findings are therefore likely to be wrong, though the latter may at least be useful for generating laboratory-based research hypotheses.

This issue’s review of pathways targetable in TCL by Epstein-Peterson and Horwitz [10] gives much material for predictions. As many of these pathways are also essential for the function of non-malignant cells in the TME, targeting them could hypothetically alter the environment in ways which could be both beneficial and harmful. The gamma/delta PI3K inhibitor duvelisib, for example, is associated with a marked decrease in immunosuppressive Tregs [11], which may improve the anti-tumor effect of cytotoxic T cells but could also remove the immunosuppressive effect of Tregs on the lymphoma itself, causing progression. Notably, there was no rapid progression seen in clinical trials, and the patients with TCL who received duvelisib in the phase 1 study [12] had sufficient response to warrant an ongoing global phase 2 trial of the drug. Still, rapid progression in TCL is not a purely hypothetical concept, as it did occur when the immune checkpoint inhibitor (ICI) nivolumab was given to patients with indolent ATLL [13] and AITL [14]. The post-hoc explanation of the phenomenon was the unintended blocking of the PD-1-driven tumor suppression maintained by PD-L1 expressed on the antigen presenting cells (APCs, Fig. 2). But this explanation could not be extended even to all types of ATLL, let alone all TCLs. In fact, as reviewed in this issue by Ishitsuka in the context of overall management of ATLL [8], there may be a role for ICIs in the more aggressive (acute and lymphoma) subtypes. The experience with ICIs in cutaneous T-cell lymphomas (CTCLs), as reviewed by Reneau and Wilcox [15], complicates matters further: many patients with Sézary Syndrome (SS), which is often PD-1-positive, responded to ICIs with an initial short-lived “tumor flare”, but were neither more nor less likely to achieve an objective response [16]. A bioplausible explanation springs to mind: that ICIs both remove the PD-1-associated suppression of the Sézary cells—causing the flare—and enhance the activity of cytotoxic T cells which, unlike in the more aggressive ATLL, can still overwhelm the “flared up” PD-1-positive Sézary cells resulting in an overall response to treatment. This is certainly a post-hoc explanation that deserves further laboratory study.

Of course, discussions about preclinical models and bioplausibility should not obscure the amount of misery TCLs bring to patients and their families, more so than most other cancers. Two particularly aggressive, incurable, and largely untreatable TCLs—hepatosplenic T-cell lymphoma and T-prolymphocytic leukemia—have recently been reviewed elsewhere [17,18]. However, the literature on the much less mentioned but no less deadly primary and secondary central nervous system TCLs is scant. Pang and Chihara try to rectify this in their review [19]. And there is some cause for optimism: we may still be in the dark about the true utility of

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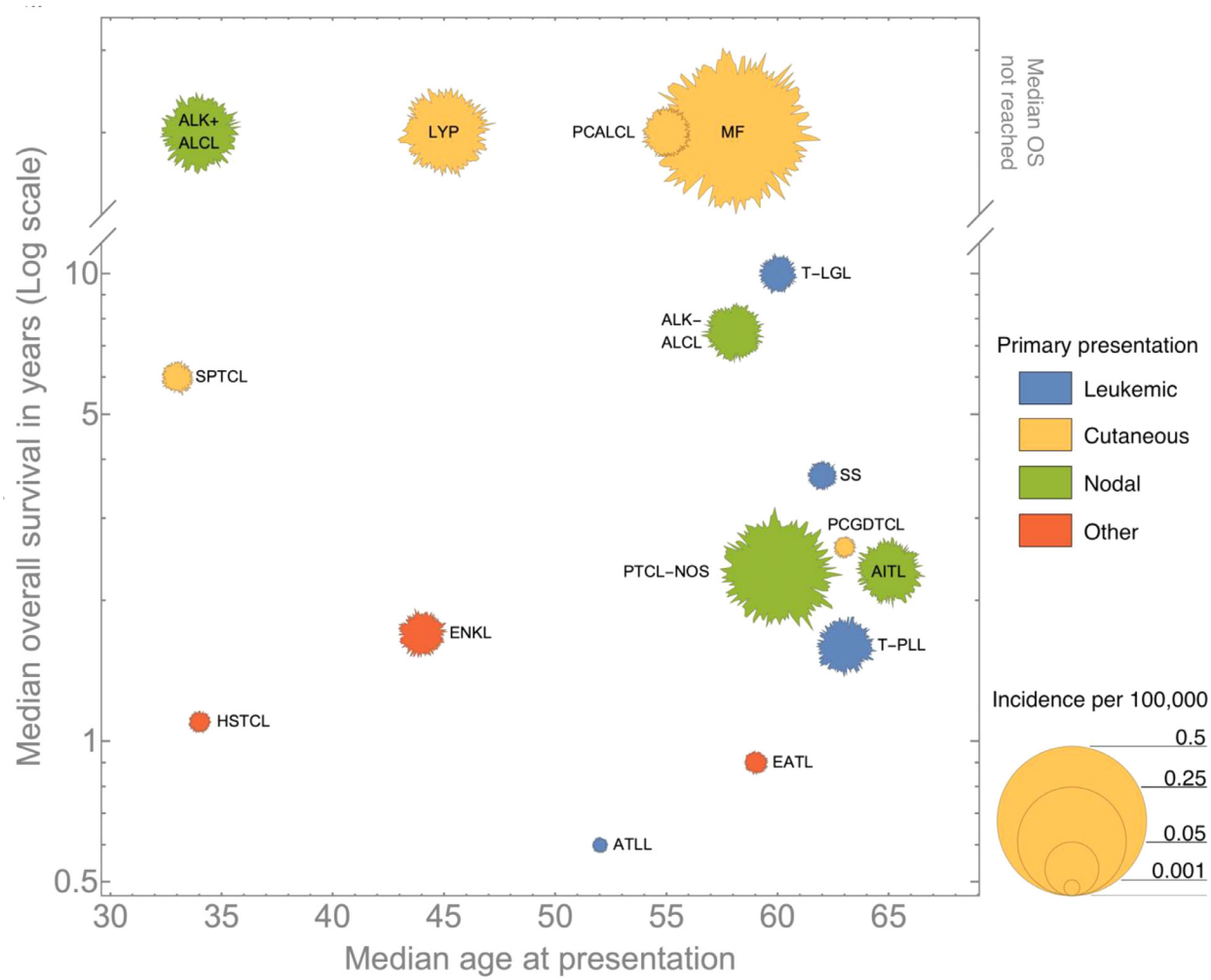

Fig. 1. The more common mature T and NK-cell malignancies according to the median age at presentation and median overall survival from diagnosis, as reported in the supplementary references. Size of the bubble is proportional to the reported incidence in the United States; jagged edges represent the uncertainty in calculating incidence for such rare disorders using incomplete case series or epidemiological data. Note that these parameters, incidence in particular, are significantly different in the rest of the world (e.g. the most common TCLs in many Asian and South American countries are ENKL and ATLL, while in North America they are almost exclusively found in first-generation immigrants from those countries). ALCL, anaplastic large cell lymphoma [24]; LYP, lymphomatoid papulosis [3]; PCALCL, primary cutaneous ALCL [24]; MF, mycosis fungoides [25]; T-LGL, T-cell large granular lymphocyte leukemia [26]; SPTCL, subcutaneous panniculitis-like T-cell lymphoma [27]; SS, Sézary syndrome [25]; PCGDTCL, primary cutaneous gamma-delta T-cell lymphoma [28]; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified [24]; AITL, angioimmunoblastic T-cell lymphoma [24]; ENKL, extranodal NK cell lympohoma [29]; T-PLL, T-cell prolymphocytic leukemia [30]; HSTCL, hepatosplenic T-cell lymphoma [27]; EATL, enteropathy-associated T-cell lymphoma [27]; ATLL, adult T-cell leukemia/lymphoma [4].

adding etoposide to anthracycline-based chemotherapy, or the effectiveness of high-dose chemotherapy with autologous stem cell rescue as consolidation, but as Nizamuddin and colleagues note in their review of anaplastic large cell lymphoma and other CD30-positive TCLs [20], there is a particularly effective treatment for this group of diseases in the form of brentuximab vedotin, with more on the way. Furthermore, molecular profiling of peripheral T-cell lymphoma not otherwise specified, until recently a waste-basket category diagnosed by exclusion, has uncovered several distinct groups with potentially targetable dependencies [21,22], as reviewed here by Malecek and Mehta-Shah [23]. These are the first and essential steps towards unraveling the complex TCL biology, developing new treatments, and bringing some clarity and understanding about these rare and heterogeneous disorders to physicians and patients alike.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

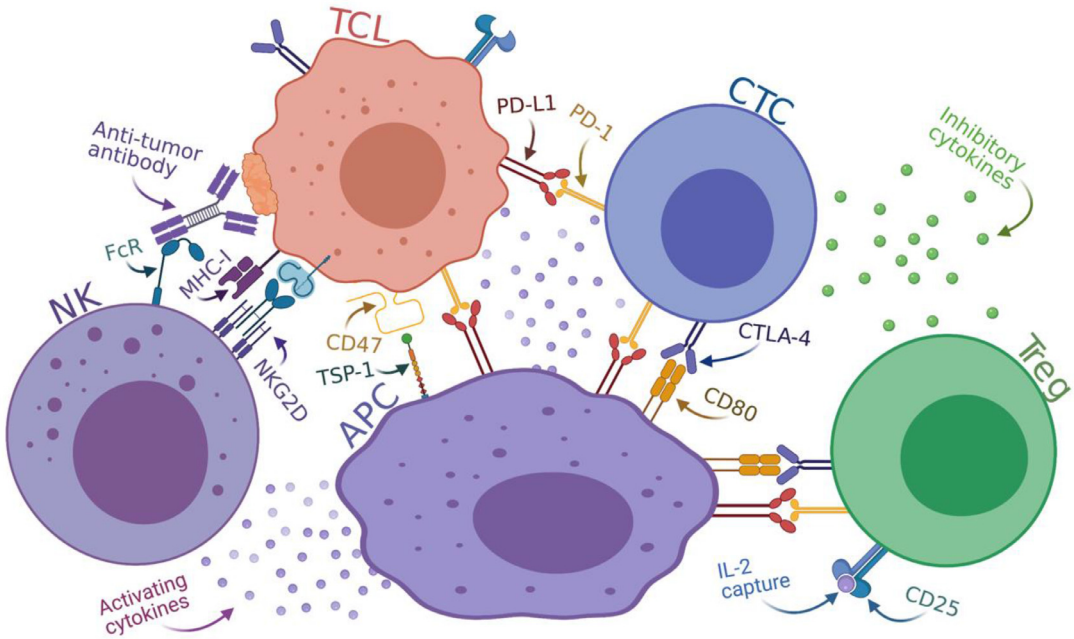

Fig. 2. An overview of just some of the interactions between T-cell lymphoma cells (TCL), antigen-presenting cells (APC), cytotoxic T cells (CTC), regulatory T cells (Treg), and NK cells (NK). Note that the TCL may express the surface proteins of any and all other cells, although some combinations are more common than others. Similarly, the active signaling pathways of the TCL may mimic those of other cells in different states of activation created with BioRender.com.

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