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Peripheral T-cell lymphoma – are we making progress?

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ABSTRACT

Peripheral T cell lymphoma (PTCL) is a rare subtype of non-Hodgkin lymphoma. PTCLs are heterogeneous in terms of biology, but generally have more aggressive features and poorer outcomes than aggressive B-cell lymphomas when treated with combination chemotherapy. While the best long-term results are still seen with intensive chemotherapeutic approaches, significant progress has been made with molecular profiling identifying genetic drivers of PTCL that could serve as therapeutic targets. Tailoring therapy to different subtypes of PTCL may lead to more individualized approaches with the hope of improved outcomes. In this paper, we review current therapies for treatment of PTCL, newly identified molecular markers, and the role of emerging therapy and novel combinations of existing agents.

1. Introduction

Peripheral T-cell lymphomas (PTCLs) are an uncommon and highly heterogeneous group of disorders, comprising about 10–15% of all non-Hodgkin lymphomas (NHL) and grouped by their common origin from mature (post-thymic) T lymphocytes and natural killer (NK) cells [1]. The physiological complexity of normal T-cells is reflected in the biology and clinical features of PTCLs, which are among the most complex areas of hematopathology and hematooncology. Until recently, the molecular mechanisms and related phenotypes of the PTCLs was poorly understood, and most therapeutic trials included all PTCL cases together in heterogeneous patient groups. Similarly, for the more common systemic forms of PTCL, upfront therapy has often followed this one size fits all approach, with intensive combination chemotherapy regimens largely derived from trials focused on the more common aggressive B-cell lymphomas.

Comprehensive genomic profiling of PTCLs has identified genetic drivers of PTCL, provided valuable insights into pathobiology, and refined our current classifications [1,2]. The identification of recurrent mutations, and the understanding that these mutations have prognostic and functional significance, is just beginning to impact therapy. As described below, our increased understanding of the biology of PTCL is currently outpacing clinical advances. However, as we more precisely define distinct molecular subsets of disease, we can provide more targeted and hopefully more effective treatments. Here, we review the recent molecular advances in some of the more common PTCLs and their impact on classification, prognosis, and treatment.

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2. Advances in understanding the biology of PTCL

2.1. Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell Lymphoma (AITL) most often presents with systemic disease and prominent constitutional symptoms. Skin rash with associated pruritus is commonly present. There is often polyclonal hypergammaglobulinemia, associated with autoimmune phenomena [1]. The neoplastic CD4-positive T cells of AITL show phenotype of follicular helper T cell (TFH) by gene expression profiling (GEP) studies and by immunophenotyping [3]. The most common TFH markers expressed by AITL include CD10, CD279 (PD-1), CXCL13, ICOS, CXCR5, and BCL6. Although AITL is a T-cell malignancy, there is often secondary expansion of B-cells and plasma cells, which likely reflects the TFH function of the neoplastic T-cells [1]. The strong association with EBV infection suggests that the virus may partially be implicated in development of AITL. TFH phenotype is also seen in one-third of PTCL-not otherwise specified (PTCL-NOS). These observations and recent genetic discoveries (see below) have led to the recognition of two other PTCL entities related to AITL: follicular T-cell lymphoma (FTCL), and nodal PTCL with a TFH phenotype (PTCL-TFH) [4]. These entities (AITL, FTCL, and PTCL-TFH) are grouped together under a common heading in the 2017 WHO classification, to facilitate clinical trials based on shared biology. This new category separates these entities from the broader category of PTCL-NOS but also keep them distinct from AITL.

Somatic mutations in epigenetic modifiers (TET2, DNMT3A, IDH2), in the RHOA pathway (RHOA), and in the TCR pathway (VAV1, CD28, PLCγ1, CTNNB1, GTF2I, PI3K) have been found in varying frequencies in AITL and PTCL-TFH [5–10]. RHOA is a small GTPase protein involved in the regulation of cell motility and polarization [8]. Among PTCLs, several recurrent RHOA missense mutations have been described. Depending on the disease entity, they can either activate or inhibit the protein activity [7]. In AITL, RHOAG17V mutations likely serve a dominant negative function, blocking RHOA GTPase activity [6,8]. IDH2 mutations are relatively specific among PTCL subtypes for AITL, occurring in 20–45% of cases, and particularly involve IDH2R172 [9]. In a study of 190 PTCLs, Lemonnier et al. found TET2 mutations in AITL (47%) and PTCL-NOS (38%) (these cases are now classified as PTCL-TFH), and rarely in enteropathy-associated T cell lymphomas (EATL) [10]. Of note, mutations involving TET2, DNMT3A, RHOA, and IDH2 often co-occur in the same case, including PTCLs in which all four of these genes are mutated [7,8]. Among these mutations, those involving DNMT3A may be particularly early events. Although the molecular pathogenesis of AITL and other TFH-derived PTCLs is incompletely understood, the relationship of the aforementioned genes to epigenetic regulation suggests that disruption of gene expression via epigenetic mechanisms is involved in disease development and/or progression, and resonates with the observed clinical activity of AITL to epigenetic modifying drugs such as histone deacetylase inhibitors.

2.2. Anaplastic large cell lymphomas

ALCL is a group of several distinct clinicopathologic entities comprising ALK-positive ALCL, ALK-negative ALCL, primary cutaneous ALCL, and breast implant-associated ALCL. All ALCL subtypes are of T-cell lineage and share common pathological features, including the presence of morphologically distinctive cells designated “hallmark” cells and uniformly strong expression of CD30 [1].

Although translocations activating ALK were among the first chromosomal rearrangements identified in lymphoma, until recently, the genetics of ALK-negative ALCL has been unknown. A recent study identified DUSP22 and TP63 rearrangements in 30% and 8% of systemic ALK-negative ALCLs, respectively [11–13]. These rearrangements were mutually exclusive of each other, and were uniformly absent in ALK-positive ALCLs [11].

The cases with DUSP22 rearrangements typically have a t(6; 7) (p25.3; q32.3) translocation. However, other partners have been identified and the significance of the partner locus is unknown [12]. Cases with DUSP22 rearrangements tend to be morphologically monomorphic, usually lacking cytotoxic granules, and appear to have a significantly better prognosis than other ALK-negative ALCLs (similar to the favourable outcomes seen in ALK-positive ALCL) [14]. DUSP22 rearrangements also can be seen in primary cutaneous ALCL, ALK-negative ALCL limited to mucosal sites, and lymphomatoid papulosis [15]. Another recurrent rearrangement identified in ALK-negative ALCL involves TP63, commonly occurring as a TBL1XR1/TP63 fusion, and seems to confer a significantly worse prognosis [11,13].

GEP studies have shown that ALK-negative ALCL has a signature similar to that of ALK-positive ALCL, but separated from other T-cell lymphomas [16]. ALK-negative ALCL often harbours convergent mutations and kinase fusions that lead to constitutive activation of the JAK/STAT3 pathway, which is also critical for the pathogenesis of ALK-positive ALCL [16]. Pharmacologic inhibition of JAK/STAT3 could be a promising strategy for the treatment of molecularly stratified ALCL, and studies of JAK inhibitors in T-cell lymphoma are underway.

ALK-negative ALCL arising in association with breast implants, a provisional entity in the 2016 WHO classification, is a unique form of this disease. It has morphologic and immunophenotypic features indistinguishable from ALK-negative ALCL, but with distinctive clinical features and behaviour [1]. Neoplastic cells are localized to the seroma cavity and/or pericapsular fibrous tissue surrounding the breast implant. The risk of developing BIA-ALCL may be confined to those with textured implants. The majority of these patients have disease confined to the seroma and interior wall of the capsule with excellent outcomes after excision alone (median overall survival 12 years) for those with localized disease. The rare patients with mass penetrating the capsule or extension to regional or distant nodes do not have the same uniformly favourable prognosis with surgery alone [17].

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