Challenges and new prospects in hepatosplenic γδ T-cell lymphoma

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Introduction
Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoid neoplasms characterized by aggressive clinical behavior and dismal prognosis. Hepatosplenic γδ T-cell lymphoma (γδ-HSTL) is a particular form of PTCL that arises from a small subset of γδ T-cell receptor-expressing lymphocytes. γδ-HSTL has a rapidly progressive course and poor outcome due to its refractoriness to conventional chemotherapeutic approaches. The very low incidence of γδ-HSTL, along with its propensity to mimic different pathological entities, makes this lymphoma a true diagnostic challenge. In this review, we highlight the biological and clinical features of γδ-HSTL that contribute to making this lymphoma a mostly incurable disease. Moreover, we provide a new insight into the crosstalk between HSTL clones and the bone marrow, liver and spleen vascular microenvironment, in which neoplastic cells reside and proliferate. We further discuss γδ-HSTL associated molecules that might be proposed as potential targets for novel therapeutic approaches.

Keywords: T cell lymphoma, peripheral T cell lymphomas, hepatosplenic T cell lymphoma, gamma delta T cell lymphomas

Abstract
Peripheral T-cell lymphomas (PTCLs) are a rare subgroup of hematological neoplasms which account for about 10% of non-Hodgkin lymphomas (NHLs) [1]. These aggressive lymphomas arise from T and natural killer cells, which, as the result of a variety of genetic aberrations, acquire a malignant phenotype [2,3]. According to the latest World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, PTCLs can be divided into specified and non-otherwise specified (NOS) forms. The particular genetic and molecular signatures typifying the former group are absent in PTCL-NOS, a subgroup indeed characterized by heterogeneous and variable morphological and phenotypic features [4]. Both groups of PTCLs show, in the majority of cases, unfavorable clinical outcome, poor responsiveness to conventional chemotherapeutic approaches and lack of effective targeted therapies. Among the different specified entities, which include angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma (ATLL), anaplastic large T-cell lymphoma (ALCL, in its ALK+ and ALK- forms), a small number of cases (<1% of NHLs) are represented by γδ T-cell lymphomas (γδ-TCLs). γδ-TCLs are extremely rare and mostly extranodal lymphomas deriving from γδ T-cells, a specific subset of lymphocytes carrying a γδ T-cell receptor (TCR) and involved in both innate and adaptive immunity [5]. γδ-TCLs can be classified into two main categories: hepatosplenic γδ T-cell lymphoma (HSTL) and primary cutaneous γδ T-cell lymphoma (PCGD-TCL). Despite the similar bleak prognosis and rapid downhill course, HSTL and PCGD-TCL show some differences in cancer cell biology and clinical features. Like other types of PTCL, γδ-TCLs are poorly responsive to anthracycline-containing regimens, which remain the front-line standard treatment for most B-cell lymphomas. For all these reasons, γδ-TCLs represent an interesting field of investigation aimed at improving diagnostic and therapeutic performances.

In this review we focus on the pathobiology and clinical features of the hepatosplenic γδ-TCLs focusing on key features, either clone-intrinsic or pertinent to the associated microenvironment, with potential diagnostic and therapeutic significance.

γδ T-lymphocytes
Double-negative T-cell precursors (CD4- CD8-) originating in the bone marrow (BM) migrate toward the thymus, where they begin their path toward maturation and acquisition of antigen recognition capability. Antigen recognition
is a finely regulated mechanism which allows the adaptive immune system to identify and discern self and non-self components complexed to major histocompatibility complex-I (MHC-I) and MHC-II molecules. T-lymphocytes are able to perform this main process through their surface TCR. TCRs have a heterodimeric structure made of two different polypeptide chains which result from rearrangement of specific genomic segments: the variable region (V), the joining region (J) and the diversity region (D), all inserted in specific genetic loci. The vast majority of T-lymphocytes (95%) express on their surface a TCRα/β (formed by one α and one β chain), while just a small minority of T cells (nearly 5%) expresses a TCRγ/δ. The presence of both TCRs on T cells is prevented by the δ-chain locus insertion into the α-chain locus (between the Vα and the Jα region); this means that rearrangement of the latter chain implies deletion of the genetic sequence coding of the former. The acquisition of an α/β rather than a γ/δ phenotype is affected by the relative signaling strength of the pre-TCRα/β and the TCRγ/δ, but also depends on bioactive molecules populating the thymic microenvironment, and involved in lineage commitment [6]. The acquisition of an α/β fate was demonstrated to be almost exclusively reliant on Notch-mediated signals. The activation of the Notch pathway, indeed, must persist after the β-selection checkpoint occurring at the DN3 stage of immature lymphocytes, driving differentiation and promoting survival of pre-T cells [7,8].

Conversely, γ/δ commitment does not seem to require a constant and active Notch signaling cascade and can occur in the absence of such signals. γ/δ differentiation is mainly influenced by other factors including fetal age, immunophenotypical arrangement of T-progenitors (DN2) or positivity for interleukin 7 receptor α (IL7Rα) and SOX-13. In about 95% of cases, all these factors are involved in TCRγ/δ signaling and actively participate in lineage commitment [9].

As two variable-region genes are commonly located inside the δ chain locus, the most representative subsets of γ/δ T-cells express either a Vδ1 or a Vδ2 receptor [10]. Such subgroups, further classified according to different immunophenotypical profile and distinct tissue localization, show dissimilar functions.

Vδ1, which represent the minority of γ/δ T-cells (about 20%), preferentially reside within the intestine, skin epithelia, uterus and spleen [11]. They are usually CD5−, CD28−, CD57+, express the naive phenotype-related CD45RA antigen and exhibit high levels of chemokine receptors CXCR4 and CCR7. Conversely, Vδ2 are mainly detected in the peripheral blood as circulating lymphocytes. They express CD5, CD28, low levels of CXCR4 and CD45RO and display a cytotoxic and memory phenotype. If appropriately stimulated, Vδ2 can also act as professional antigen-presenting cells [12]. This last property underlines the dual role of such T cells in both the adaptive and innate branches of the immune system and implies a high degree of functional plasticity [13,14]. Such an innate role is confirmed by the ability of γ/δ to elicit an immunological response after exposure to non-protein molecules such as phosphoantigens produced by several bacteria and protozoa, plants and tumor cells [15] through the expression of Toll-like receptor (TLR) isosforms.

**Hepatosplenic γδ T-cell lymphoma**

**Etiology and pathogenesis**

In 1990, Farcet and colleagues described a novel type of T cell aggressive lymphoproliferative disorder occurring in liver and spleen, which shared sinusoidal localization as well as the expression of a TCRγ/δ in the neoplastic cells [16]. In 2001, HSTL was listed as an independent unique pathological entity in the World Health Organization classification of tumors of hematological and lymphoid tissues.

The etiology of HSTL is unknown. Nonetheless, some clues emerge from case report analysis. Interestingly, a considerable number of patients have a clinical history of immunodeficiency and persistent antigenic stimulation [17].

In most cases HSTL is related to immunodeficiency due to immunosuppressive treatments (mostly cyclosporin and/or azathioprine) given after solid-organ transplant [18,19]. In addition, a susceptibility to T-cell NHLs and in particular to HSTL is observed in patients with autoimmune disorders such as inflammatory bowel diseases (mostly Crohn’s disease), rheumatoid arthritis and psoriasis undergoing immunosuppressive treatment with tumor necrosis factor α (TNFα) inhibitors combined with thiopurines. However, recent data do not show a direct association between T-cell NHLs and TNFα inhibitors used alone [20].

Genetic analysis and cytogenetic studies proved that genetic abnormalities such as isochromosome 7q (i7q), trisomy 8 and loss of Y chromosome are associated with HSTL [21,22], although their actual role in the neoplastic transformation of γδ T cells is unclear; gene expression profile analyses have, furthermore, demonstrated that both αβ and γδ forms of HSTL share a molecular signature recalling typical NK genetic arrangement together with an overexpression of the activated form of the spleen tyrosine kinase (Syk) [23].

A causal relationship between exposure to malaria parasites, which cause a chronic antigenic stimulation, and HSTL has been suggested in patients with impaired immune functions [24].

The role of Epstein–Barr virus (EBV) is not entirely clarified; its effects in HSTL may be mediated by its capability to provide a constant and chronic antigenic stimulation which results in a sustained activation of γδ cancer cells [25]. Unlike B-cell lymphoproliferative disorders, EBV genome positivity is sporadic and can be found only in a minority of already transformed γδ T-cells, suggesting that EBV infection does not have a critical role in HSTL pathogenesis, but at most represents a late event [26]. Only in one case has a direct association with hepatitis B virus (HBV) infection been reported, and as with EBV, HBV-DNA cannot be detected in tumor cells [27].

**Clinical features**

HSTL is an uncommon form of PTCL which usually arises from γδ T cells and primarily affects young male adults with a median age of 34 years (range, 16–58 years; male/female [M/F] ratio, 5:1) [17,28], although a minority of cases show positivity for the TCRα/β isofrom. The HSTL α/β subtype shares its dismal prognosis with the γ/δ variant, but shows different epidemiologic features, i.e. a female predominance...
and a slightly higher median age (range, 13–50 years; M/F ratio, 1:3.6) [29,30].

The diagnostic approach to this lymphoproliferative disorder is challenging. The clinical presentation, consisting of hepatomegaly and splenomegaly in the absence of overt lymphadenopathy, can be shared by many other pathological conditions. Moreover the very low incidence of this neoplasm (fewer than 200 cases reported since 1990) [31,32] does not ensure a prompt diagnosis.

Patients affected by HSTL typically present with systemic symptoms including fever, weight loss, night sweats and fatigue. Physical examination reveals splenomegaly in virtually all cases and hepatomegaly in about 50% of cases [28,32]. Lymphadenopathy is extremely rare in HSTL [33]. Peripheral blood examination often reveals moderate cytopenia with anemia and decreased platelet count; in advanced stages of disease severe neutropenia can also occur, associated with a predisposition to systemic infections [34,35].

The mechanisms causing anemia are not fully understood [36], but increased spleen size [37] and/or myelophthisis probably contribute [38]. Along with anemia and/or thrombocytopenia, patients frequently show a mild increase in liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP]) and in lactate dehydrogenase (LDH) levels, the former related to hepatic sinusoid infiltration by neoplastic cells, which could be mistaken for hepatitis [39,40], the latter related to the hemolytic anemia.

Hemophagocytosis is commonly reported in HSTL and, if conspicuous, can often culminate in overt hemophagocytic syndrome (HPS) [41,42], a pathological condition consisting of excessive macrophage activation leading to an aberrant phagocytosis of mature and precursor blood cells [43]. Such uncontrolled macrophage activation has been related to an excess of proinflammatory cytokines such as TNFγ and interferon γ (IFNγ) [44–48]. Moreover, γδ T cell subsets represent a source of the proinflammatory chemokine IL17 [49], which can activate macrophages and whose role in the engendering of proinflammatory conditions was reported in lymphoproliferative diseases including angioimmunoblastic T-cell lymphomas [50] and in autoimmune disorders [51]. The development of HPS could also hypothetically involve the interaction between macrophages and extracellular matrix components, remodeled by neoplastic γδ T cells. Indeed, it has been demonstrated that in skin epithelium, γδ T cell-induced hyaluronan deposition in the extracellular matrix (ECM) can mediate macrophage recruitment. The preferential distribution of γδ T-cells within the vascular niches of hematopoietic and hemocatheteric organs (i.e. BM, spleen) can therefore be directly linked with the enrichment in activated macrophages with detrimental erythro- and hemophagocytic function [52].

**Diagnostic issues**

Early detection of HSTL is of paramount importance, since prompt treatment represents the only chance of achieving a temporary control of disease evolution. Unfortunately, in the vast majority of cases, the diagnosis is made in the advanced stage, owing to the misleading clinical picture at presentation. Among the various entities able to mimic HSTL, both B and T lymphomas including splenic marginal zone lymphoma (SMZL), hairy cell leukemia (HCL), mantle cell lymphoma (MCL), lymphoplasmacytic lymphoma (LPL), B-cell prolymphocytic leukemia (B-PLL), diffuse large B-cell lymphoma (DLBCL), micronodular T-cell/histiocyte-rich large B cell lymphoma (MTLCL) and T-cell large granular lymphocytic (T-LGL) leukemia should be mentioned. All of these disorders share a usual “primary splenic” presentation with splenomegalgy, peripheral blood (PB) and/or BM involvement, in the absence of prominent lymphadenopathy. As splenomegaly can be observed in several different pathological conditions, it cannot be considered per se pathognomonic for HSTL [53,54]. Since patients with HSTL are commonly febrile on presentation, they usually undergo extensive screening for infectious diseases, which can delay the diagnosis. The most important step in the diagnosis of HSTL is suspecting HSTL. Indeed, following the formulation of a HSTL hypothesis, an accurate diagnosis can be achieved through a straightforward diagnostic algorithm that may include the analysis of spleen, BM, liver and PB. Morphological examination of blood smears, BM and/or liver biopsies followed by flow cytometric phenotyping performed on peripheral blood and bone marrow aspirates [55] represent useful diagnostic tools when splenectomy cannot be performed. The immunophenotypic profile of γδ-hepatosplenic lymphoma usually includes positivity for the γδTCR/CD3 complex, CD2 and CD7, while CD4, CD5 and CD57 are often negative. The neoplastic cells commonly display a cytotoxic profile associated with the expression of CD16 and CD56 with variable CD8 expression [54]. As previously reported, the presence of i7q is frequent in cases of HSTL. As a consequence of this chromosomal aberration, a loss of one of the TCRγ alleles and duplication of one TCRβ allele may occur. Molecular investigations to detect TCRγ rearrangement represent an additional diagnostic tool to be combined with immunophenotypical analysis [56].

**Histopathology**

γδ-HSTLs are mainly composed of a neoplastic mostly medium-sized cell population with scattered cells ranging from small to large, the small cells showing medium-sized oval nuclei, sometimes indented, with irregular contours and chromatin ranging from loosely condensed to coarse. Nucleoli, when present, are basophilic, small and inconspicuous. Lymphomatous cells are characterized by a pale and basophilic cytoplasm with indistinct cell borders and occasional fine granules; large cells with blastic morphology can be detected as a side-population of the medium sized neoplastic cells or, more rarely, may represent the entire clone. Such blastic cells can frequently be observed already at the time of diagnosis, although they are commonly associated with a terminal “blastic” transformation.

On diagnosis, neoplastic infiltrates typically involve bone marrow, liver and spleen, where they show a prevalent intrasinusoidal/intravascular localization.

The pattern of bone marrow infiltration may vary considerably during the course of the disease. On diagnosis, the bone marrow biopsy typically shows a hypercellular marrow with trilinear hyperplasia and large hyperlobated
megakaryocytes, associated with a variable, often subtle, neoplastic intrasinusoidal infiltration. This picture can be observed even in patients with overt anemia and thrombocytopenia. In the advanced phase, the early intrasinusoidal pattern is associated with an increasingly interstitial distribution of blastic and large neoplastic cells.

On gross examination, the spleen is enlarged and dark purplish-brown. Splenic parenchyma appears completely effaced with a marked hyperplasia of the red pulp due to the presence of neoplastic cells, of small and medium size, inside the splenic sinuses and the cords. Along with diffuse involvement of the red pulp, the white pulp appears atrophic or completely absent [57].

The hepatic pattern of infiltration is quite similar to the initial phase of bone marrow involvement; the normal hepatic architecture is preserved in the majority of cases and the portal triads are spared. Neoplastic small-to-medium atypical cells classically settle in contact with the endothelium of the sinusoids, which appear only slightly enlarged. Due to this tumor distribution, the organ function is usually maintained.

Lymph node involvement is extremely rare and can be characterized by either infiltration of the lymph node sinuses by neoplastic cells or diffuse effacement of the cortical and medullary areas.

Role of the microenvironment

Studies regarding γδ-T cell lymphomas have so far neglected the functional crosstalk between tumor lymphocytes and endothelial components, assuming that such neoplasms are scarcely reliant on the surrounding microenvironment. To date no experimental data or animal models able to provide a clearer picture of this interaction are available. In this review, we speculate on some possible mechanisms underlying the connection between HSTL clones and stroma basing our considerations on studies regarding the biology of normal γδ-T cell counterparts.

The well-known and particular localization of γδ lymphoma cells in bone marrow, liver and spleen parenchyma is likely due to at least two causes: first, the physiological abundance of γδ T cells in liver and spleen in comparison with peripheral blood; second, the constitutively high expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM) in sinusoidal endothelial cells [58,59]. Analysis of the vascular dynamics possibly involved in such pronounced γδ-T cell clone tropism may therefore lead to the identification of mediators involved not only in adhesion mechanisms but also in clone survival.

The interaction with the sinusoids is mediated by ligands expressed by the endothelium which are recognized by receptors expressed on neoplastic γδ-lymphocytes; their engagement triggers the release of tumor-cell proinflammatory cytokines (e.g. IL1β and TNFα) which in turn activate endothelia [60–62].

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or CD44 (homing cell adhesion molecule, HCAM), which share a common signaling pathway, may be followed by a downstream activation of Akt and phosphatidylinositol 3 kinase (PI3k) [68], two key regulators of prosurvival signaling. Moreover, PSGL-1 is able to drive slow rolling of lymphocytes by activating Src and Syk kinases through interaction with E-selectin [69] and to activate the extracellular signal-regulated kinase (ERK) pathway [70] involved in T-cell proliferation [71,72].

Together with PSGL-1 and CD44, VLA-4 could also play a protective role favoring tumor γδ-lymphocyte survival. Neoplastic cell homing may be driven by the axis involving the stromal-derived factor-1 (SDF-1/CXCL12) and its receptor CXCR4 expressed on Vδ1 T lymphocytes. Indeed, a high amount of CXCL12 produced by stromal or endothelial cells is found, respectively, in BM and spleen or liver [65,73,74]. Unexpectedly, although the thymus is a well known producer of CXCL12 [75], its involvement in HSTL is not usually reported [4]; lack of thymus infiltration may be explained by two reasons: first, HSTL primarily affects young adults and the thymus is subjected to a physiological age-related involu-ration; second, CXCL12, which plays a necessary but possibly not sufficient role in lymphocyte recruitment, is produced only by stromal cells of the cortex, which reside far from the vascular areas [76].

The malignant clone could finally sense CCL21 and CCL25 through CCR7 and CCR9, respectively, which have been reported to drive its tissue localization [77,78].

The liver shows an intrasinusoidal pattern of infiltration too, probably owing to the expression of specific adhesion molecules shared by both bone marrow and liver vascular niches [79]. Among the diverse adhesion pathways, the axis relating to lymphocyte function-associated antigen-1 (LFA-1)/ICAM-1 seems to play a key role, as demonstrated in acute lymphoblastic leukemia (ALL) [80]. Although CD11a is not expressed in γδ tumor cells [81], its role as adhesion molecule may be replaced by the mutual ICAM-1 receptor CD11b. A gene expression profiling analysis carried out on γδ-T cell lymphoma samples showed that both natural killer (NK) and neoplastic γδ-T cells express cytotoxic activity. The ICAM-1 receptor CD11b, expressed in both classes of lymphocytes, was shown to play an important role in maintaining NK survival, exerting antiapoptotic effects by activating the Src–β-catenin–ERK pathway and leading to increasing levels of bcl-2 [82]. Similar effects might be mediated by CD11b on γδ-lymphoma cells after binding to extracellular matrix components such as fibronectin. As demonstrated in an in vitro model, undamaged hepatocytes are able to stimulate endothelial cells to express adhesion molecules and thus drive normal lymphocyte recruitment [83]. In light of the preserved hepatic parenchyma in HSTL, the intrasinusoidal localization of tumor cells may be based on the same mechanism.

Finally, in spite of the splenic architecture disarrangement due to neoplastic infiltration, sinuses lining cells are capable of mediating adhesion events by the surface exposition of mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) together with the classical endothelial adhesion molecules [84–86].

Current treatments and new perspectives

Management of hepatosplenic T-cell lymphoma is difficult due to its refractoriness to either single or combined chemotherapeutic agents classically used in NHLs. Splenectomy may be of some benefit in the management of HSTL, although it does not modify the natural history of the disease. Indeed, it has been demonstrated that splenectomy eliminates the risk of a splenic rupture, and it ameliorates peripheral cytopenia (often due to hemophagocytosis), reducing the risk for hemorrhage [54,87].

Several treatment approaches have been proposed over the years, with variable but overall disappointing results. In 2000, Weidmann reported 45 patients with HSTL who had...
received a variety of chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine and prednisone/CHOP; methotrexate, leucovorin [LV], doxorubicin, cyclophosphamide, vincristine and prednisone/MACOP; MACOP plus bleomycin) with or without splenectomy or bone marrow transplant. The study showed that only a minority of patients (20%) achieved a complete remission. No cures were reported and the average survival time was 8 months [32]. A similar report on 21 patients receiving a more homogeneous first-line treatment highlighted a slight increase of complete remissions with a comparable average survival rate [28]. The most recent retrospective study, published in 2009, reported a complete remission rate of 50% among 14 patients treated with classical induction regimens (CHOP; fractionated cytoxan, liposomal doxorubicin, vincristine and dexamethasone/HyperCVIDDoxil) [33]. All three studies confirmed the same low rate of durable response to regimens containing anthracyclines such as CHOP and CHOP-like regimens [88].

The use of cladribine has also been proposed in the past, but, except for sporadic case reports of successfully treated patients, no clinical benefit was reported [89–91]. An Italian group proposed an alternative therapeutic approach based on pentostatin (2′-deoxycoformycin), a purine analog inhibitor of the adenosine deaminase (ADA), administration. Effects were encouraging due to the striking cytotoxicity activity of pentostatin against tumor cells and modest myelotoxicity compared to common treatments; nevertheless, only a very slight increase in median survival rate was reported without any durable complete remission [92]. Most recently, Voss and colleagues suggested that a non-CHOP alternative regimen containing ifosfamide, carboplatin and etoposide (ICE) or ifosfamide, etoposide and high-dose cytarabine (IVAC) followed by autologous or allogeneic stem cell transplant (SCT) consolidation is able to improve survival [93]. The benefit of allogeneic transplant, presumably by virtue of graft versus leukemia (GVL) effects, was also documented in a retrospective study by Le Gouill et al. in 77 cases of aggressive T-cell lymphoma (including three cases of HSTL) [94].

Finally, regimens based on the administration of a single agent such as romidepsin or pralatrexate are currently under evaluation. These initial studies were performed in large and heterogeneous groups of relapsed/refractory PTCLs and show some encouraging results, but, unfortunately, to date we have no specific data regarding the possible use and effectiveness of these drugs in HSTL [95,96].

Targeted therapies based on the use of monoclonal antibodies (mAbs) have proven to be an effective tool, significantly improving survival and the clinical course of several hematological neoplasms. The prototypical example is rituximab, an anti-CD20 mAb which has radically changed the prognosis of some B cell lymphomas expressing the surface molecule CD20 [97,98].

To date, one candidate proposed for the treatment of T cell neoplasms has been the surface molecule CD52, target of the mAb Campath (alemtuzumab). However, the use of alemtuzumab in PTCL management did not achieve notable results in terms of overall survival, probably because of the heterogeneous and highly variable expression of CD52 on lymphoma cells [99]. To date, the combination of Campath and CHOP chemotherapy has been flawed by the high relapse rate in patients with PTCLs [100]. Similar results were reported also in HSTL, where the anti-CD52 mAb used in association with inhibitors of ADA did not significantly improve survival [101]. Moreover, some encouraging data about use of zanolimunab (human anti-CD4 mAb) have emerged from a phase II clinical study performed in relapsed or refractory PTCLs. However, given that γδ-HSTL clones are often negative for CD4, a therapeutic approach based on the administration of anti-CD4 mAbs should probably be excluded in this lymphoma [102].

On the basis of the bilateral relationship between the vascular niche and γδ-tumor lymphocytes, targeting of molecules involved in adhesion events is an attractive option: in light of the known PSGL-1 expression on activated T-cells and of its role in inducing activated T-cell apoptosis upon mAb-mediated cross-linking [103], CD162 could be a suitable candidate target, already proposed in multiple myeloma management [104], for mAb immunotherapy in HSTL: the hyaluronic acid receptor CD44 is overexpressed on γδ-lymphocytes and actively mediates T lymphocyte rolling on activated endothelium [105], as such representing an additional potential candidate even if no data regarding the development of anti-CD44 drugs for clinical use have been reported.

Finally, in light of the results obtained with recent gene expression profile analysis investigations, oral administration of Syk inhibitors may represent a new therapeutic opportunity [23,106].

Conclusions

HSTL is a very rare neoplasm which represents a real challenge both for the diagnostic approach and for its clinical management. Moreover, the particular biology characterizing the clone together with its poorly understood relationship with the surrounding microenvironment make HSTL a captivating field of investigation. To date, all classic chemotherapy regimens have shown disappointing results and no therapeutic protocol has been universally accepted. We have focused our attention on the role that microenvironmental components may have in supporting cancer survival and progression, since a more detailed elucidation of such multifaceted dynamics may permit identification of suitable candidates for multitargeted and more effective therapies.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahelathcare.com/lal.

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