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Pathogenesis and therapy of cutaneous lymphomas – Progress or impasse?

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Abstract: The cutaneous environment hosts a number of hematopoietic neoplasms that are dominated by primary cutaneous (PC) T-cell lymphomas. Recent progress in molecular biology and immunology has provided tools to investigate the pathogenesis and the biology of these neoplasms. This review highlights newest findings concerning the immune biology of $CD4^+CD56^+$ hematodermic neoplasms, and PC T-cell and B-cell lymphomas, speculating how these can be translated into more sophisticated, biology-based treatment approaches in the near future.

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Introduction

The skin is the second most common site of extranodal non-Hodgkin lymphomas after gastrointestinal tract. The annual incidence is estimated to be around 1 in 100 000 persons.

Primary cutaneous (PC) lymphomas typically demonstrate a clinical behavior and prognosis differing from that of the histologically similar nodal lymphomas, which may involve the skin secondarily. Therefore, it makes sense to classify cutaneous non-Hodgkin lymphomas separately from other non-Hodgkin lymphomas. In the last decades, controversies on the best way to classify these diseases have been a major drawback for interested researchers who have tried to provide more data on different lymphoma entities. Important progress that needs to be acknowledged today is the agreement between dermatologists and pathologists achieved in the new WHO/EORTC classification (1,2). This classification distinguishes between cutaneous T-cell lymphomas, cutaneous B-cell lymphomas, and so-called 'precursor hematologic neoplasm', i.e. $CD4^+/CD56^+$ hematodermic neoplasm (HN). New data on different lymphoma subgroups have been shaping and will continue to shape this classification. In contrast to T-cell-derived tumors, little is known about (immuno)biology of the latter two groups. A continuing effort is required that will provide more insight into the pathogenesis of PC non-T-cell lymphomas and stimulate the development of therapeutic strategies to efficiently treat these tumors (Fig. 1).

The WHO classification was primarily based on data obtained by clinical (immuno)histologic and genomic analysis of nodal lymphomas. The clinically based EORTC classification, on the other side, was triggered by the observation of dermatologists and dermatopathologists that many cutaneous lymphomas did not fit the descriptions given in the WHO classification. For instance, the EORTC-classified PC follicle center-cell lymphomas do not generally express BCL-2 and are not typically associated with t(14;18) translocation [as their counterpart, WHO-classified nodal follicle center lymphomas (FCLs)] but show an excellent prognosis and high responsiveness to radiotherapy with relatively low voltage. The new consensus WHO-EORTC classification reconciles the two systems

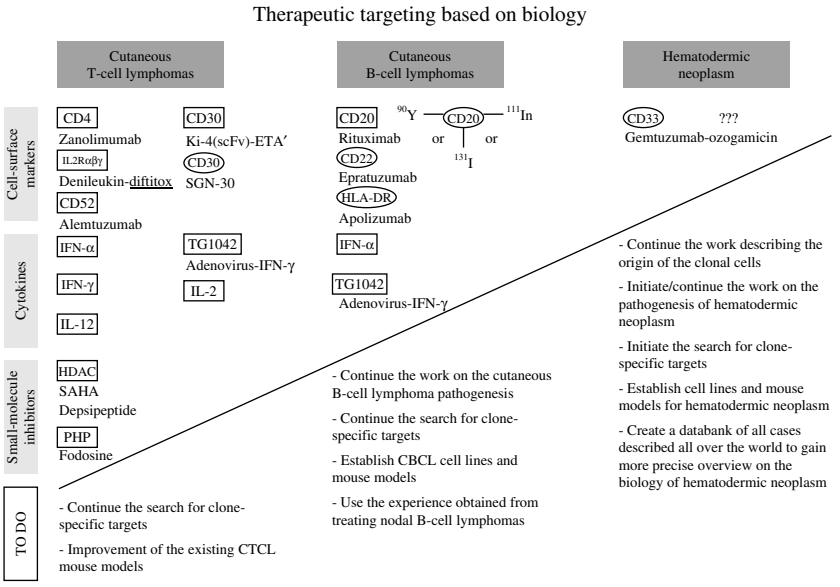

Figure 1. Representation of the therapeutics deducted from the biology of cutaneous lymphomas. Rectangles represent substances tested in cutaneous lymphoma, whereas ellipses represent substance tested in (extra)nodal lymphomas, but not specifically in cutaneous lymphoma. The generic name of each compound is listed below the corresponding graphic symbol. IL, interleukin; IFN, interferon; HLA, human leukocyte antigen.

and takes into account the sometimes completely different clinical behavior of cutaneous lymphomas from histologically similar systemic lymphomas which occur secondarily in the skin. The new system has been validated on more than 1900 patients' data of the Austrian and Dutch Cutaneous Lymphoma registries. In the CTCL group, the three major groups, mycosis fungoides, Sézary syndrome, and PC $CD30^+$ lymphoproliferative diseases, make up to more than 90% of all CTCL, whereas the remainder have been reclassified in more details in the new system. This will no doubt facilitate more urgently needed comparative clinical studies and molecular analysis of the remaining 10% of CTCL with a poorer prognosis. Importantly, the group of peripheral T-cell lymphomas, unspecified, has been reduced by the removal of several provisional entities (PC-aggressive epidermotropic $CD8^+$ T-cell lymphoma, the cutaneous gamma/delta T-cell lymphoma, the PC $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma), underlining the progress in molecular and immunohistochemical analysis of these tumors.

The reclassification of the cutaneous B-cell lymphomas recognizes now the PCFCL as a distinct entity. In particular, the definition of the follicular as well as the diffuse growth pattern of these lymphomas with excellent prognosis will help prevent false recognition and over-treatment of the diffuse large-cell PCFCL. On the contrary, the EORTC-based subgroup of the PC large B-cell lymphoma of the leg has been included in the WHO-EORTC classification (PCLBCL, leg type). Separation of this group based on location of the lesion has been criticized, but clinical and molecular studies have confirmed its distinction from the PCFCL. As it became clear over the years that this more-aggressive large-cell lymphoma does not only occur on the lower extremities, it is a matter of time when this nomenclature will change into a more pathogenesis-based one, for example based on BCL-2, BCL-6, CD10, or MUM1/IRF4 expression pattern. As for now, the term 'leg-type' indicates a molecular and prognostic entity rather than the anatomic location of the tumor. Taken together, the WHO-EORTC classification seems to turn into an invaluable connection between the dermato-oncologists and hematologists/oncologists involved in the treatment of cutaneous lymphomas. Uniform diagnosis and, hence, larger patient study groups will help shape and optimize treatment of these rare diseases. Molecular analysis of the various and more concisely defined entities will fine-tune the new classification system that, let us be clear at this point, reflects merely the latest state of error. Nevertheless, the new WHO-EORTC classification should be used by all clinicians and pathologists involved in the care of our lymphoma patients who now can fully profit from its clear advantages over the two former controversial and sometimes contradictory classifications.

Trying to point out the shortcomings of the new classification is difficult. Future classification will include the experience of clinicians and pathologists from outside of Europe and thus elucidate geographic variations of frequencies and biology of cutaneous lymphomas. Rare and difficult-to-diagnose entities such as the neutrophil-rich variants of $CD30^+$ anaplastic large-cell

lymphoma (ALCL) may be included; the importance of cases of clonal pityriasis lichenoides and its potential notion as a lymphoma entity may be analyzed in more details. The rare PC lymphoblastic lymphoma cases may be evaluated and included in future classification. As has been pointed out by others, coding systems such as the International Classification of Diseases for Oncology will need to include the new entities defined in the WHO-EORTC classification to foster comparative studies in the future.

Highways and byways in the ontogeny of $CD4^+CD56^+$ HNs

$CD4^+CD56^+$ HN represents an entity that has only recently been recognized and appropriately classified (1). $CD4^+CD56^+$ HN is characterized by highly aggressive behavior and poor prognosis (median survival of 14 months), presentation in the skin followed by lymph node and bone marrow involvement, often terminating in a leukemic phase. Since the early nineties, several case reports or small series of $CD4^+CD56^+$ malignancies have been reported as distinct entities using a myriad of different names [reviewed in (3)]. On the basis of the lymphoid morphology of tumor cells, expression of CD56 [also known as neural cell adhesion molecule (NCAM)], absence of T-cell receptor or surface CD3, a natural killer (NK) origin has been evoked by many despite the negativity of most NK-associated markers and the absence of azurophilic granulations. These and similar findings prompted inclusion of these $CD4^+CD56^+$ malignancies into WHO classification under the name blastic NK cell lymphoma without further evidence of an NK-cell origin (4). At that time-point, it seemed less important that CD56 expression has often been observed outside NK-cell lineage, for example in acute myeloid leukemia, myeloma, or T-cell lymphoma [reviewed in (3)]. Furthermore, the presence of CD4 was almost blindly accepted as a part of the new entity, although CD4 expression is not compatible with a NK origin, because it has never been described on normal NK cells at any stage of differentiation (5). In light of increasing number of reports dealing with this subject, one question imposed itself eventually – What cells do these $CD4^+CD56^+$ HN originate from?

The answer to this question was a matter of debate until recently. Chaperot et al. were first to show that leukemic $CD4^+CD56^+$ cells express a constellation of markers very similar to the one present on the plasmacytoid dendritic cells (pDCs), that is lack of common lineage markers with concomitant expression of CD123/interleukin (IL)-3 receptor α-chain, HLA-DR, and CD45RA (6). Several other studies followed confirming this initial report as well as demonstrating the expression of additional molecules shared by pDC, like lymphoid protooncogene, TCL1, and cutaneous lymphocyte-associated antigen (CLA) (7,8). pDCs represent a newly identified DC subset, characterized by plasma cell-like morphology and unique surface phenotype ($CD4^+CD68^+CD123^+BDCA\text{-}2^+HLA^-DR^+$) in the absence of common lineage (hereafter referred to as 'lin') markers (CD3, CD11c-, CD13, CD14, CD16, CD19, CD20, CD34, CD56) (9,10). pDCs are thought to be the key component in innate antiviral immunity due to their capacity to produce large amounts of type I interferons (IFN) (9). Whereas CD4, CD45RA, CD68, CD123, and HLA-DR can be expressed on other lymphoid or myeloid cells, BDCA-2 is the only to date known marker specifically expressed on human pDC. BDCA-2 is specifically expressed by resting blood and bone marrow pDC and is lost during maturation (11). $CD4^+CD56^+$ HNs seem to share similar immunophenotypic profile – lin-, $CD4^+$, $CD45RA^+$, $CD68^+$, $CD123^+$, $HLA\text{-}DR^+$, $BDCA\text{-}2^+$, and $BDCA\text{-}4^+$ (6,12–14) apart from CD56 expression. Even though normal pDCs are considered to lack common lineage markers such as CD56, there are reports showing CD56 expression in a subset of blood pDC (15) or its induction by Flt-3 ligand treatment in healthy individuals (16). Latter lead to the hypothesis that HN may be a proliferation of malignant pDC with an activated $CD56^+$ phenotype influencing their leukemic and migratory potential (16), for example to skin (CLA expression) or to central nervous system (NCAM expression).

Chaperot et al. have shown on several occasions that leukemic pDC not only share the phenotype, but they also share the functional features of normal pDC because they (i) produce IFN-α upon virus stimulation; (ii) survive and differentiate into functional DCs in response to IL-3/G-CSF/CD40L/virus; and (iii) elicit TH1- or TH2-type response depending on the nature of the stimulus (6,13,17). Evidence of MxA protein expression, which is a surrogate marker for lesional type-I IFN activity, in $CD4^+CD56^+$ tumors further supports their pDC-like phenotype (14,18). A certain case-to-case heterogeneity has been observed, although, in IFN-α production and MxA expression. These differences may

be attributable not only to malignant transformation but also to the different cell activation/maturation stage corresponding partly to mature or to resting pDC. Namely, pDCs lose the capability to produce type I IFN upon maturation and instead become fully mature DCs capable of inducing T-cell proliferation (9).

Although tumor cells in HN per definition should lack conventional lineage markers, increasing number of reports showing different exceptions to this rule led to an open discussion on the ontogeny of these cells. Myeloid origin was favored by some because HN (i) express myeloid markers such as CD33, CD36, and CD68 (6,12–14); (ii) have demonstrated transformation in leukemia of myelomonocytic lineage (7,19); and (iii) were associated with myelodysplastic syndrome before the diagnosis of $CD4^+CD56^+$ leukemia was made (12,19,20). Lymphoid origin was, on the contrary, preferred by others due to (i) occasional expression of lymphoid surface molecules such as CD2, CD5, and CD7 (6,12–14); (ii) expression of TCL1, a feature shared with normal pDC (7,8); and (iii) lymphoid transcripts such as pre-T cell receptor-α (pT-α) and λ-like 14.1 (6) and the fact that analogous findings have been reported for normal pDC (9). Interestingly, normal pDC are shown to up-regulate low levels of myeloid antigens like CD13 and CD33 upon activation (10), delivering another 'pro' argument for their lymphoid origin. There have been suggestions that the precursor involved in the malignant/leukemic transformation may be more immature than blood pDC, given an overtly blastic morphology of leukemic cells and low CD45 expression (6).

Ultimately, one cannot escape the thought that all the efforts directed toward elucidating the ontogeny of HNs may end up in the discussion about the origin of pDC. Given the available experimental evidence, pDC appear to represent a unique hematopoietic lineage, whose development may be much more flexible than the one of conventional lymphoid- and myeloid-committed cells (9). Particularly, because it has been shown that virus infection can program bone marrow plasmacytoid DCs to differentiate into myeloid DCs (21).

Is there progress in CTCL?

Mycosis fungoides and Sézary syndrome as most frequent CTCL behave as indolent neoplasms with a very wide variation in clinical presentations. This group is also the most investigated one. CTCL are characterized by an accumulation of clonal T lymphocytes in the cutaneous microenvironment that are responsible for many (immuno)pathologic phenomena. For the purpose of length and clarity, some of these phenomena will be addressed. The malignant population is represented in well-differentiated mature memory $CD3^+CD4^+CD45RO^+CD7^{variable}$ T cells that home into the skin and retain the capacity to regulate immune functions (1). Malignant T cell in CTCL has been shown to express skin-homing receptors CLA and CCR4, where latter binds to skin-manufactured ligands CCL17 [also known as thymus and activation-regulated chemokine (TARC)] and CCL22 [also known as macrophage-derived chemokine (MDC)], known to be overexpressed in CTCL [reviewed in (22)]. Furthermore, malignant T cells in patients with Sézary syndrome appear to express functionally active CXCR4 receptor that binds to constitutively expressed CXCL12 (also known as stromal-cell derived factor (SDF) 1) in their destination, the skin (23). This is associated with the lack of CD26 expression, which is the enzyme dipeptidylpeptidase IV that is responsible for proteolytic inactivation of SDF-1 (a finding already described in CTCL) and is probably facilitating homing of malignant cells to the skin.

On the basis of cytokine profile, malignant CTCL cells are predominantly displaying T-helper (TH)-2 cytokine profile dominated by IL-4 and IL-10 that results in the local and systemic dysbalance of the TH1/TH2 system (24,25). *In situ*, IL-10 protein co-localizes with expression of the tolerance-inducing, non-classical HLA molecule, HLA-G (26). HLA-G is able to hamper antitumor immune response by inhibiting different cell types including dendritic cells as well as immune effector cells, such as $CD8^+$ T cells or NK cells (27,28). On the basis of this concept, one may speculate that the future therapeutic approaches will focus on targeting (minimizing or counteracting) the expression or trying to modulate/shift cytokine profile of tumor cells in the dermal compartment (e.g. with cytokines, see below). In this way, correction of immune deviations would also abolish induced HLA-G expression and subsequently its immunosuppressive activities. Moreover, CTCL cells seem to express the whole palette of other immune inhibitory molecules such as p140/KIR3DL2 and ILT2, which, apart from the inhibition of NK and T-cell cytotoxicity, can also mediate CTCL cells' resistance to apoptosis (29). The production of IL-10 together with transforming growth factor (TGF)-β is thought to perpetuate

immaturity of surrounding dendritic cells that show enhanced phagocytosis of apoptotic CTCL cells. This, in turn, results in the presentation of apoptotic (antigen) material to $CD4^+$ CTCL cells via MHC II molecules which are in this way triggered to become regulatory T cells. These regulatory T cells contribute to the general immune suppression observed in CTCL, and they also produce IL-10 and TGF-β closing the vicious circle that stimulates dendritic cell immaturity and enables CTCL growth (30).

In early stages, CTCLs have an indolent nature primarily affecting only the quality of life due to the skin symptomatology, whilst in later stages, they start to behave like true hematological malignancies, requiring appropriate systemic treatment. Characterization of chromosomal abnormalities during the progression of the disease showed evidence of microsatellite instability followed by frequent genetic aberrations on chromosomes 1, 6, and 11 as well as changes on chromosomes 8 and 17 (31,32). It is of note that oncogene c-myc and tumor suppressor gene p53 are located on chromosomes 8 and 17 and appear to play an important role in the advanced disease change due to respective gene mutations. Apart from structural chromatin changes resulting in the dysregulation of cell-cycle control genes (i.e. p53), alteration of key genes involved in the control of apoptosis (dysfunctional new splice variant of Fas protein) (33) and telomere length (high telomerase activity) (34) was implicated to play a role in the pathogenesis of CTCL.

Cutaneous B-cell lymphomas – Where do we go now?

The majority of human lymphomas (95%) originate from B lymphocytes, with the rest belonging to T-cell malignancies (35). This may come as a surprise, given the similar frequency of B and T cells in human body. In the skin, however, the situation appears to be reversed, with primary B-cell lymphomas being far less frequent than primary T-cell lymphomas (20 versus 80%, respectively) (1). This might reflect the fact that B lymphocytes rarely reside in the skin, except in infectious conditions such as borreliosis or lues. Most PC B-cell lymphomas (CBCL) are considered low-grade neoplasms. Follicular center (FC) lymphomas and marginal zone (MZ) lymphomas represent the most common disease entities in this group (11 versus 7%, respectively) (1). PC diffuse large B-cell lymphomas (leg type), which typically demonstrate aggressive clinical behavior, are quite rare (<1% of all cutaneous lymphomas).

Molecular studies have provided evidence of an ongoing germinal center cell reaction in PC FC and PC MZ lymphomas by showing ongoing mutations in the rearranged immunoglobulin-variable gene regions (35). Furthermore, high-throughput gene expression profiling showed that low-grade B-cell lymphomas demonstrate a gene expression signature of germinal center cell B cells, whereas aggressive diffuse large B-cell lymphomas showed a gene expression profile reminiscent of activated B lymphocytes (36). This implies that the therapeutic approaches for these two biologically distinct groups should target different molecules/cells to achieve an efficient response.

There are a number of genetic abnormalities involving transcriptional factors and oncogenes such as BCL2, BCL6, MYC, and JUNB that seem to play a role in the pathogenesis of cutaneous B-cell lymphomas (37). Furthermore, there is evidence of the inactivation of the tumor suppressor genes p15 and p16 (38). Chromosomal translocations/gene mutations affecting various genes like CCND1, API2, MALT1, FOXP1, PAX5, ATM, CD95 (Fas), TP35, SOCS1, IKBA, and IKBE, shown in other nodal and extranodal lymphomas may prove to be of importance in CBCL as well. Clinical observations that primary CBCL regress after antibiotic therapy have resulted in the hypothesis of an infectious origin of CBCL (39). *Borrelia burgdorferi* appears to be involved in the pathogenesis of some CBCL types, at least in Europe (40).

Jazirehi and Bonavida (41) have recently summarized cellular and molecular events induced during the treatment of extra cutaneous B-cell lymphomas with an anti-CD20 antibody, rituximab. This in-depth analysis on the use of this chimeric antibody in the treatment of various B-cell lymphoma types has resulted in an improved understanding of the biology of B-cell lymphomas. Besides expected anti-B-cell effects mediated through complement activation and antibody-dependent cellular cytotoxicity, rituximab appears to have direct effects on B-cell viability via selective down-regulation of antiapoptotic factors in mitochondria. It diminishes the activity of the p38 MAPK kinase-signaling pathway resulting in the inhibition of the IL-10/IL-10R autocrine/paracrine cytokine autoregulatory loop. This, in turn, results in the inhibition of the constitutive STAT3 activity and subsequent down-regulation of BCL2 expression. Down-regulation of BCL2 underlies the chemosensitization phenomenon, frequently

observed during the combined use of rituximab with chemotherapy.

Despite some data on the molecular aberrations associated with CBCL pathogenesis, little evidence exists concerning the immune biology of these heterogeneous diseases. If there are speculations on the existence of other infectious agents (42) except *B. burgdorferi*, these need to be looked for, because we might face healing of the skin lymphomas with adequate antimicrobial therapy. Additionally, or even consequently, the search continues for the trigger that induces and supports the ongoing germinal cell reaction in the mixed cellular infiltrate of CBCL. Furthermore, the most important signal transduction pathways activated need to be fully dissected to allow specific molecular interventions with, for example, different small-molecule inhibitors. However, in this field, researchers are considerably slowed down by the lack of *in vitro* models (e.g. CBCL-derived cell lines) and by the difficulties in the identification and the culturing of the tumor cell population.

The art of treating – the call is on pathogenesis

$CD4^+CD56^+$ HNs

At this moment, tumor cells in HNs are considered to be a malignant counterpart of normal pDCs. Aggressive clinical course and dubious prognosis have led to conclusion that these neoplasm could be best treated with regiments used in acute leukemia, alternatively associated with radiotherapy and bone marrow transplantation (1,43). Nevertheless, despite aggressive treatment and initially induced remission, quick relapse unresponsive to further chemotherapy frequently follows making the prognosis poor. Comparative trials are still missing. We believe that the key to the most optimal treatment of these tumors lies in their biology (Fig. 1). Stimulated tumor cells demonstrate fundamental functional properties that link them unequivocally to pDC lineage – IFN-α production in response to viruses, capability to induce T-cell proliferations as well as TH1 or TH2 biasing, secretion of various cytokines, and chemokines upon stimulation (3,13). Interestingly, maturation and differentiation of these 'malignant pDC' is not blocked *in vitro*, hence, that could give rise to functional mature DCs under appropriate stimulation (6,13). This may prove to be of therapeutic interest; however, to mount an efficient antitumor response, one must ensure that the activated T cells are TH1 rather than regulatory T cells. Further insights into biology of these rare tumors seem to provide new treatment options, like the use of gemtuzumab ozogamicin (humanized anti-CD33 antibody linked to the potent antitumor antibiotic calicheamicin), because the cross-linking of cell-surface bound anti-CD33 monoclonal antibody renders leukemic pDC sensitive to apoptosis (13).

PC T- and B-cell lymphomas

Immense progress has been made in the targeted biological therapy of PC T-cell and B-cell lymphomas (Fig. 1) (44). Various recombinant TH1-skewing cytokines, such as IFN-α and IFN-γ, IL-2 and IL-12, are nowadays almost routinely used to treat CTCL in the clinics [for review see (22,45) and Fig. 1]. We will try to focus now on the newest (immune/patho)biology-based therapeutic options. For example, gene therapy-mediated induction of antitumor response and stimulation of TH1 arm through adenovirus-mediated gene delivery of IFN-γ seems to work for CTCL and even more impressively for CBCL (46). In CTCL, so-called 'IFN resistance' may even stimulate the TH2 profile, because clonal T cells from patients with Sézary syndrome fail to respond to the TH1-skewing treatment with either IFN-α or IFN-γ. Various defects in the IFN-signaling pathway seem to underlie this 'resistance' phenomenon (47–50). By a serendipity, IFN resistance can be successfully targeted by replicating viruses, such as measles virus, that use the defects in the IFN-signaling cascade to lyse the tumor cells that are no longer able to mount an efficient antiviral response (47,48).

Advances in recombinant protein technology have enabled the development of different therapeutic monoclonal antibodies and fusion molecules as shown in Fig. 1. Some of the compounds shown in the figure will be highlighted. Zanolimumab is a high-affinity fully human antibody that targets CD4 on T cells that has entered phase III development for CTCL (51). Alemtuzumab is a humanized immunoglobulin-G1 directed against CD52, a glycosylated peptide antigen expressed on most malignant B and T cells (52). Anti-CD20 antibodies are now conjugated with various radionuclides (e.g. indium-111, yttrium-90, or iodine-131) and applied with/or without chemotherapy in relapsed patients or patients with refractory disease (44). Two additional antibodies targeting other

molecules on B cells, such as CD22 (epratuzumab) and HLA-DR, are currently being assessed in clinical trials.

Small-molecule inhibitors represent a new class of agents that are able to inhibit different kinases, transcription factors, antiapoptotic molecules – virtually anything described as 'dysfunctional' in cancer. Bortezomib is a proteasome inhibitor that induces apoptosis through the inhibition of ubiquitin–proteasome pathway that has been tried in different lymphoma types (44). Seliciclib (CYC202, R-roscovitine) is a selective inhibitor of cyclin-dependent kinases that may prove to be of use in mantle-cell lymphoma (53). Another way to inhibit expression of unwanted molecules is represented in the antisense oligonucleotide technology. Oblimersen (G3139) is such a substance that blocks the expression of BCL2 that has shown encouraging activity in patients with mantle-cell lymphoma.

Molecules such as histon deacetylases (HDAC) play the key role in maintaining chromatin structure and regulation of gene expression. Recent studies indicate that abnormal histone deacetylase activity may lead to aberrant, i.e. overexpression of oncogenes and down-regulation of tumor-suppressor genes and antiproliferative molecules. In leukemias, HDACs have been linked to the activity of translocated oncoproteins and the suppression of gene expression necessary for normal differentiation (54). Suberoylanilide hydroxamic acid (SAHA) and the cyclic peptide, depsipeptide (FR-901228), belong to the group of histone deacetylase inhibitors (55). They present challenging therapeutic compounds for patients with both solid tumors and (extra)nodal lymphomas. Fodosine (BCX-1777) is an inhibitor of PNP phosphatase, an enzyme maintaining DNA synthesis during T-cell proliferation that is currently tested in T-cell malignancies, including CTCL.

The list of new promising substances in the treatment on nodal lymphomas is getting longer and longer every day representing a good sign of progress. Similar development in the field of cutaneous lymphomas, even though impressive and manifold, appears to lag behind, probably due to indolent nature of these tumors. The implementation of high-throughput analysis techniques for the genome and proteome will enable the discovery of new processes/dysfunction important in the pathogenesis and following classification of cutaneous lymphomas. The experience shows that some of the currently hip compounds as well as their potential benefit in a given disorder were discovered by serendipity or through a simple translation to a similar disease group. We therefore hope and are quite optimistic that cutaneous lymphomas will experience similar development and adopt some of the approached developed in the brotherhood of nodal lymphomas.

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