Current Epigenetic Therapy for T-Cell Lymphoma

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Introduction

Cutaneous T-cell lymphoma (CTCL) is challenging to treat. Patients with advanced disease typically only enjoy brief responses to conventional chemotherapeutics, and are at particularly high risk of infectious complications during the treatment with chemotherapy. Combination and intensification of conventional chemotherapeutics fails to cure the vast majority of patients of patients with CTCL or other forms of peripheral T-cell lymphoma (PTCL). In this context, biological agents, and in particular the histone deacetylase inhibitors (HDACis), present an attractive alternative because they lack many of the side effects of conventional chemotherapy and appear to overcome chemotherapy resistance.

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The HDACis target not only the epigenome but also numerous nucleic and cytoplasmic non-histone proteins and are powerful and selective inducers of cancer cell apoptosis and modifiers of the tumour microenvironment. To date, the best data for their use comes from trials in the lymphoid malignancies and CTCL is the only condition for which HDACis are currently registered. The FDA has approved romidepsin and vorinostat for use in relapsed/refractory CTCL and these agents provide patients with a new opportunity for durable clinical response. Similarly, romidepsin has potent activity in nodal PTCLs, with emerging data supporting a future role in clinical practice, either alone or in combination with conventional therapies.

Here we discuss the concept of epigenetic modifying agents, briefly review the putative targets for the HDACis and discuss key clinical trials supporting their use in T-cell lymphoma.

Epigenetics and Epigenetic Therapies

The term "epigenetics" refers to changes in gene expression that are not coded in the DNA sequence itself, which are heritable in the progeny of cells after mitosis [1]. Epigenetic therapies, therefore, target the dysregulated gene expression of neoplasia by altering the structure of chromatin or DNA promoter regions, rather than by addressing defects in the primary DNA code of conventional oncogenes or tumour suppressor genes.

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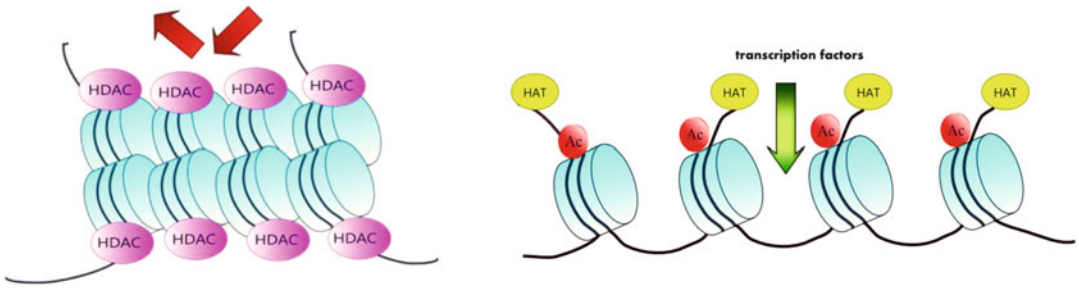

Figure 16.1 HDACs remove acetyl groups from the lysine tails of histones. Conversely HATs result in histone hyperacetylation, open chromatin formation and increased accessibility of target genes to transcription factors.

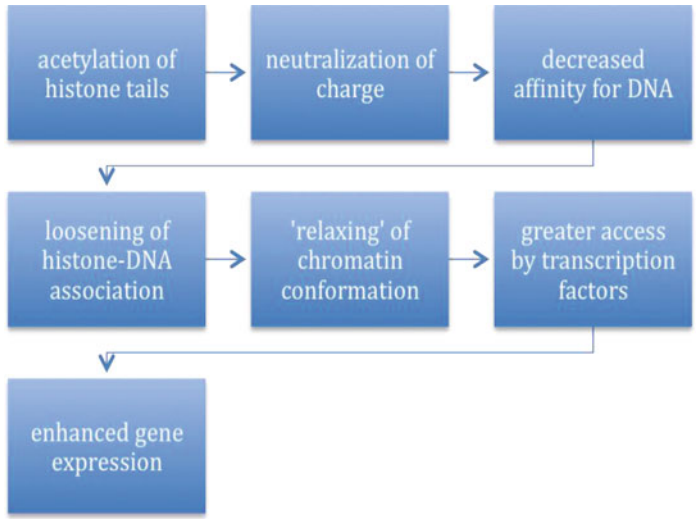

Figure 16.2 Relaxation of chromatin leads to increased gene expression

Drugs in clinical use today target two epigenetic mechanisms. Methylation of the CpG dinucleotides in the promoter regions of genes is heritable and suppresses gene expression. This mechanism is targeted by the DNA-methyltransferase inhibitors azacitidine and decitabine. The DNA demethylating agents are predominantly used in myeloid malignancies although trials continue in the lymphoid malignancies, particularly in combination with other agents. The HDACis are a broad and novel class of agents that target one aspect of the "histone code," lysine-acetylation. Histones are octomeric proteins largely responsible for the structure of chromatin and the packaging of DNA within the cell. Condensed chromatin results in tightly packaged DNA, limiting access to transcription factors. A variety of modifications to the histone tail, including acetylation, methylation, ubiquitination, phosphorylation and sumoylation, alter histone charge and subsequently chromatin structure and gene expression [2]. The archetypal and most successfully druggable example applying to all of the agents in this chapter is histone acetylation. The key enzymes involved are histone acetyltransferases (HATs) and histone deacetylases (HDACs), which have contradictory effects on the acetylation status of histones and on chromatin structure [1]. Histone acetylation by HATs results in neutralisation of charge, decreased affinity for DNA, loosening of the histone–DNA interaction and open chromatin structure—making it more accessible to transcription factors and enhanced gene expression. (figure 16.1, and 16.2) [3] Conversely, histone

deacetylation by HDACs leads to a more compact chromatin structure and gene repression. Following this logic, the HDACi could be considered de-repressors of gene expression, although in truth they have a far more complex set of effects and are probably best considered *modulators* of gene expression.

Targets of HDACi

Histone Targets

HDACs can be grouped according to their structure and homology to yeast enzymes. Classes I, II and IV are the zinc-dependent. Class III HDACs are the NAD-dependent deacetylases, sirtuins, which are not targets of the HDACis in current clinical use. Class I enzymes (HDAC 1,2,3,8) are found primarily in the nucleus, as is the single member of class IV, HDAC 11. Class II can be divided into two subgroups, IIa (HDAC 4,5,7,9) which can shuttle between the nucleus and cytoplasm, and IIb (HDAC 6,10) which is predominantly cytoplasmic [4]. Knowledge of the specific function of each HDAC isoenzyme (and therefore the effect of inhibition) continues to accumulate, but distinguishing the individual properties can be a difficult undertaking given the complexity of the cellular pathways involved. (Figure 16.3) One useful property of HDAC inhibition is that transformed cells are more sensitive to their pro-apoptotic effect than normal cells [4]. This is probably due to the dependence of malignant cells on HDACs for tumour cell growth, differentiation and apoptosis that provide a differential survival advantage [5].

HDACis share a common mechanism of action in binding a zinc ion critical to HDAC function. At present, the simplest method of grouping HDACi is based on specificity. HDACis which inhibit most or all zinc-dependent HDACs (pan-HDAC inhibitors) include the hydroxamic acid derivatives (trichostatin A, vorinostat [SAHA],

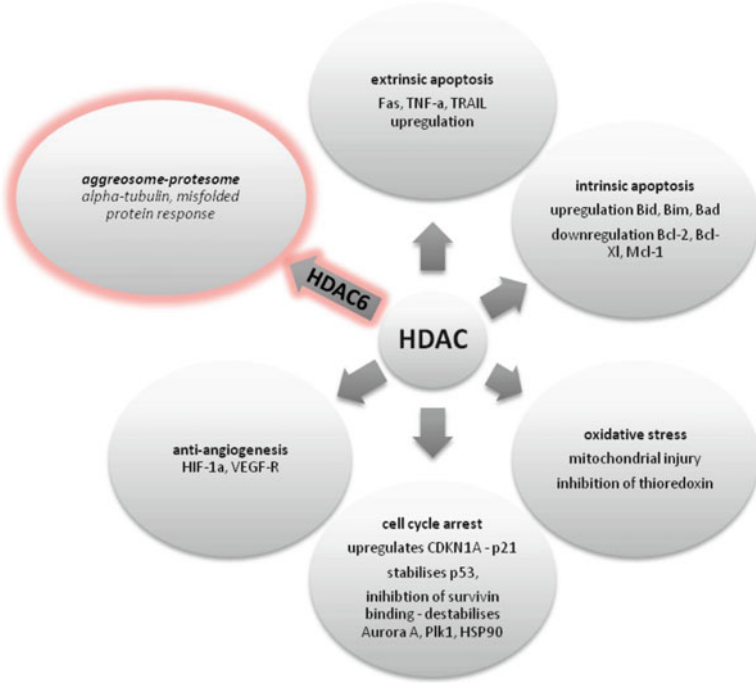

Figure 16.3 Exposure to HDACi leads a wide spectrum of biological effects including induction of apoptosis, inhibition of angiogenesis, induction of cellular senescence and disruption of the aggresome/Proteasome and endoplasmic reticulum.

panobinostat [LBH589]). Class I-specific HDACis include benzamide derivatives (entinostat, mocetinostat) and cyclic tetrapeptides (romidepsin [previously called depsipeptide]) [6]. These are summarised in Table 16.1. Cytoplasmic HDAC6 has effects on cell motility and proteasome and aggresome pathways which, along with inhibition of HDACs 1 and 2, is considered to be responsible for much of the anti-cancer effects of these drugs [6]. A key difference between the pan-HDACs and the class 1-specific HDACis is thought to be the inhibition of cytoplasmic HDAC6.

In cancer cells, HDACis induce caspase-dependent cell death, apparently through increased expression and activation of pro-apoptotic members of the intrinsic pathway (bax, bim, bak, etc.) and down-regulation of BCL-2 pro-survival proteins [7–12]. HDACi may induce sensitivity of cells to death-receptor pathway-induced apoptosis; this appears to occur either through increased expression of death receptors [13, 14] or thorough mechanisms independent of death receptor expression [15–17].

In addition to apoptosis, HDACis induce cell cycle arrest at G1/S or G2/M through a number of mechanisms including, in particular, the induction of p21. [18–21] They also induce reactive oxygen species. [22–24]

Non-Histone Targets of HDACs

The effects of HDACi on non-histone targets may be more important than direct changes in chromatin modification for anti-tumour effect [25]. Putative non-histone targets of HDACs include the STAT proteins, alpha-tubulin, HSP90, NF-KB and more controversially, p53. [6, 26]

An important way in which inhibition of HDAC6 may induce cell death is through disruption of the misfolded protein response (MPR). The MPR is a three pronged pathway which protects the cell from the accumulation of misfolded proteins that arise from defective protein synthesis [27]. Protein folding occurs in the endoplasmic reticulum, and requires the chaperone function of HSP90. [28, 29] Misfolded proteins accumulate into aggresomes by means of an HDAC6-dependent microtubule, and are then earmarked for destruction by the autophagosome. [30] This system thereby serves as a homeostatic mechanism which protects the cell from proteosomal dysfunction [6] and suggests the appeal of synergistic anti-cancer activity between proteasome inhibitors and HDACis. [31] HDACis induce both acetylation and dysfunction of HSP90, and disruption of the aggresome through acetylation of the tubulin. This is part of the rationale for the use of HDACi in myeloma; however, despite the evidence for HDACi causing dysfunction of the aggresome–proteasome pathway [32] clinical studies of HDACi have shown the class I-selective HDACi romidepsin can rescue patients with bortezomib-refractory myeloma. [33] Moreover, there is no suggestion that this potential mechanistic difference between the pan-HDACi and the isotype-selective HDACi effects the response rates in other cancers: as we shall show, response rates to the pan-DAC inhibitor vorinostat in CTCL are similar to those of romidepsin. [34] Key pharmacokinetic properties of the approved agents are listed in table 16.2.

Mechanism of Action in T-Cell Lymphoma—Biomarkers and Hypotheses

It is probable that the importance of these various mechanisms of action differs by disease being treated, and remarkable that the diseases most responsive to HDACis bare profound immunological and cytokine-signalling perturbation. The accessibility of the skin for biopsy means that CTCL provides an opportunity for the study of the effects of HDACis on tumour cells, in vivo, giving us more insights than other types of malignancy allow.

In CTCL, STAT3 phosphorylation is increased in a cytokine-independent manner, possibly as a consequence of defective T-cell receptor signalling [35–40]. Duvic and colleagues explored the mechanisms of action of HDACi using immunohistochemistry on primary patient samples in the phase II study of vorinostat [11, 41]. They showed that phospho-STAT3 was increased in the

Table 16.1 Classes of DAC inhibitors, their HDAC targets and HDAC cellular distribution. HDACs 6 and 10 are typically found in the cytoplasm [68]; however, both have also been found in the nucleus and are likely to affect transcription. [69, 70]

		HDAC specificity											
	HDAC Cellular distribution	Nuclear				Nuclear, cytoplasmic				Cytoplasmic [1]		Nuclear	
	HDAC Class	I				IIa				IIb		IV	
HDACi class	HDAC	1	2	3	8	4	5	7	9	6	10	11	
Short chain fatty acids	Butyrate												
	Valproate												
Hydroxamic acid derivative	Trichostatin A												
	Vorinostat (suberoylanilide hydroxamic acid, SAHA)												
	Panobinostat (LBH589)♣												
	Belinostat (PXD101)												
	Tubacin												
Benzamide	Entinostat (MS-275)												
	Mocetinostat (MGCD0103)												
Cyclic tetrapeptide	Romidepsin (depsipeptide)												

[Reprinted from Dickinson M, Johnstone RW, Prince HM. Histone deacetylase inhibitors: potential targets responsible for their anti-cancer effect. Invest New Drugs 2010;28 Suppl 1:S3–20. With permission from Springer Science+Business Media.]

Table 16.2 Pharmacokinetic properties of registered HDACis

	Vorinostat PO [71–73]	Romidepsin IV [74, 75]
t1/2	1.5–2 h	3 h
Protein binding (%)	71	>90
Metabolism	Hepatic (glucoronidation)	CYP3A4, 5 (minor)
Excretion	<1% intact drug excreted renally	66% excreted in bile in pre-clinical models
Bioavailability	43%	N/A

cytoplasm and the nucleus of lymphocytes and keratinocytes at baseline in all patients in whom biopsies were performed. Repeat immunohistochemistry after 4 weeks of treatment showed reduced levels of phospho-STAT3 in the nucleus in 9 of 11 patients with clinical improvement and in only 3 of 16 who did not show a clinical improvement. Interestingly, overall pSTAT-3 was *increased* in the cytoplasmic compartment, suggesting that vorinostat does not alter expression of pSTAT3, but rather it impedes its ability to translocate to the nucleus and function as a transcription factor. Fantin [11] went on to examine more baseline samples and suggested that patients with higher baseline nuclear p-STAT3, and baseline nuclear p-STAT1 were likely to be resistant to vorinostat. Researchers investigating the mechanism of panobinostat using in vitro and in vivo models, have suggested that vorinostat resistance in particular CTCL cell lines could be overcome by panobinostat, via reduction in the overall quantity of activated p-STAT3 in cells [42, 43]. These findings have not been replicated by other investigators and the differences in methodology make it difficult to make definitive statements about the precise effect of HDACi on STAT3 signalling; however, it is reasonable to conclude that reduced STAT3 signalling represents both a potential mechanism of action and resistance for HDACi in CTCL and further investigation is required.

In addition to the observations on STAT3, the immunohistochemical work of Duvic et al. showed that thrombospondin 1, an inhibitor of angiogenesis, is upregulated after exposure to vorinostat, supporting the hypothesis anti-angiogenic effects are important to HDACi activity in CTCL. [41] Work from *Ellis* et al. [44] has provided further support for the anti-angiogenesis hypothesis. They performed serial gene-expression profiling on samples from ten patients with CTCL treated with panobinostat and showed consistent changes in expression in a set of 23 genes, including down-regulation of expression the angiogenic genes GUCY1A3 and ANGPT1.

Following a genome-wide loss of function screen on cell lines which suggested that cells with higher expression of RAD23B/HR23B [45], Khan and colleagues went on to show that patients whose tumours had higher levels of expression HR23B by immunohistochemistry at baseline were more likely to have responsive disease. HR23B has a ubiquitin-like domain and shuttles proteins to the proteasome for degradation. The finding supported the concept that disruption of the proteasome is important in CTCL, and the authors suggested that it could be a useful biomarker. Further studies elucidating the precise mechanism and whether romidepsin exerts a similar effect are required.

Clinical Studies

Cutaneous T-Cell Lymphoma

The selection of CTCL and PTCL as a candidate diseases for the HDACi came through results from conventionally designed, broadly inclusive clinical phase I trials as opposed to a clear preclinical rationale. [46] HDACi therapy induces objective responses in a significant minority of patients, in the order of 25–30% across studies. The responses take a median of 8 weeks and up to 2 years to occur, and appear to last somewhere between 6 months and a year in responding patients; however, median treatment duration was in only about 3 months across the studies.

A proportion of patients benefit from protracted clinical responses as well as significant improvements in more subjective symptomatic end-points such as erythema and pruritis. This comes at the cost of other symptoms such as asthenia and gastrointestinal side effects, as well as reversible thrombocytopenia, which appear to vary between the various HDACis and doses administered.

Response Criteria

Consensus response criteria for CTCL have only recently been published, but warrant discussion here because variations in response criteria affect interpretation of studies of CTCL [47]. The new consensus criteria incorporate a composite assessment of responses in the skin, blood, nodes and viscera. Cutaneous response criteria utilise changes in the mSWAT tool (Table 16.3) [48] in which overall body surface area involvement and disease type is incorporate in the overall score. Unfortunately all CTCL response criteria are somewhat subject to inter-observer variability. An important aspect of the consensus criteria is that responses, including progression, require confirmation at least 4 weeks after the initial observation. This stipulation prevents patients coming off-study due to a temporary disease flare or the typical minor clinical fluctuations characteristic of CTCL.

The studies presented here all precede the release of the consensus criteria and so the trials of HDACi in CTCL are difficult both to interpret, and to compare with each other. (Table 16.4) Interestingly, some do not incorporate visceral responses, and others do not include the mSWAT. For example, criteria for progression in the panobinostat study mandated patients come off study after minor progression (25% increase in mSWAT) which after a deep response might still represent a significant improvement over the patient's baseline condition. The authors of the conventional response criteria do not provide a single agreed measure of the pruritis that accompanies Sézary syndrome. Choice of that endpoint varies across the studies presented here but most commonly a 30 mm or 30% reduction in a 100 mm visual/analogue scale was considered as consistent with a significant clinical symptomatic response.

Table 16.3 *The mSWAT (modified severity weight assessment tool).* Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin; plaque = any size lesion that is elevated or indurated; crusting, ulceration or poikiloderma may be present tumour = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep; Tumour = infiltration in the skin and/or vertical growth. [47, 48]

Body region (%BSA)	Patch*	Plaque*	Tumour*
Head (7)			
Neck (2)			
Anterior trunk (13)			
Arms (8)			
Forearms (6)			
Hands (5)			
Posterior trunk (13)			
Buttocks (5)			
Thighs (19)			
Legs (14)			
Feet (7)			
Groin (1)			
Subtotal of lesion BSA			
Weighting factor	X 1	X 2	X 4
Subtotal lesion BSA x weighting factor			
mSWAT score = summation of each column line above			

Table 16.4 Response assessment methods varied considerably in studies of all patients in studies of CTCL

Drug	First author	Notes on response assessments
Vorinostat	Olsen [50]	Skin: mSWAT [48]
		PR: 50% reduction in mSWAT
		CR:100% clearing of skin disease
		PD: 25% worsening of mSWAT from baseline or ≥50% increase in SPD of nodal disease
		Date of relapse: mSWAT score from nadir to a more than 50% difference between the baseline and the nadir
		Confirmation of CR/PR: ≥4 weeks
		Confirmation of SD: not defined
		Pruritis: VAS with 30 mm reduction for at least 4 weeks considered significant, with no increase in use of anti-pruritis medications
		Separate reporting of nodal response, not reported in overall response results—≥50% reduction in nodal disease or ≥25% reduction in blood tumour burden
	Duvic [41]	Physician's Global Assessment of Clinical Condition (PGA) [76]
		PR: ≥50% improvement in either BSA or skin score with reduction of lymph nodes or blood when involved
		PD: ≥25% increase in the number or area of clinically abnormal nodes, or % of BSA or new visceral disease or increase in circulating Sézary cells
		Pruritis: 30% reduction of VAS for 4 weeks
		Confirmation of CR/PR: 4 weeks
		Confirmation of SD: 8 weeks
		Confirmation of PD: 4 weeks
Romidepsin	Whitakker [52]	LN: RECIST [77]
		Skin: Composite of SWAT [48] score and erythroderma scores. [78]
		PR: 50% improvement in the *sum of* Cheson, SWAT and erythroderma scores but with ≥30% improvement in skin, and no worsening at any site
		PD: new cutaneous or non-cutaneous tumour or >25% improvement in the sum of the three assessments or ≥15% worsening of skin
		CR: response at all sites
		Pruritis: VAS with 30 mm reduction for at least two cycles considered significant.
	Piekarz [51]	Skin or Viscera: RECIST [77]
		LN: IWG/Cheson [56]
		Erythroderma: present or absent
		Flow presence: present or absent
		PR: either a response in the skin or lymph nodes
		CR: a response in all sites of disease
Panobinostat	Duvic [53]	Skin: mSWAT, PGA
		Lymph nodes: Confirmatory CTs were performed to excluded disease progression in the nodes at the time of response in the skin
		PD: ≥25% increase in mSWAT compared to nadir
		Confirmation of progression not required

Abbreviations: PGA Physician's global assessment of clinical condition, mSWAT-modified severity weighted assessment tool

Efficacy

Vorinostat

Vorinostat (suberoylanilide hydroxamic acid, SAHA) was the first HDACi approved by the FDA, in 2006, for patients with CTCL who had failed two prior systemic therapies. [49] Clinical response data came from two phase II studies: a pivotal, single-arm study of 74 patients [50] and a smaller 3-arm, sequential, non-randomised study that recruited 33 patients to treatment on one of the three treatment schedules of vorinostat. [41]

In the pivotal study by Olsen et al., subjects received 400 mg/day, now the FDA-recommended dose. 61 of the 74 patients (82%) had clinically advanced disease, 30 (40.5%) had Sézary syndrome and all had been exposed to two (median 3) prior systemic therapies: 96% to oral bexarotene; 64% to interferon and 60.8% to systemic chemotherapeutics. Reported response rates were limited to cutaneous responses, and based on reductions in the mSWAT. Although baseline computed tomography scans were performed, and visceral disease monitored during the study, formal response criteria and response data did not include visceral disease. (Table 16.4) The overall response rate was 29.7% (95% CI 19.7–41.5) and a response was seen in a third of patients with Sézary syndrome; however, only 1 patient experienced a complete remission. (Figure 16.4) An additional 48% had a measurable disease improvement (See diagram). Pruritis improvement (rather then resolution) was experienced by a third of the 65 patients who recorded a score of 3 or above at baseline. Responses occurred after a median of 8 weeks and lasted a median of 6.1 months.

Duvic et al. simultaneously conducted a second study, exploring 3 dose levels of vorinostat. Patient characteristics were similar to the pivotal study by Olsen. Patients were sequentially enrolled into the open dose level: 400 mg daily ($n=13$), 300 mg bd 3,4 or 5 days a week ($n=11$) and 300 mg bd x 14 days, with 7 days rest, with 200 mg bd maintenance ($n=9$). Each of these doses had been established as MTDs in previous phase I studies. The overall response rate was comparable between the three dose levels, although was perhaps poorer for the intermittent dosing schedule (group 2). The overall response rate was 24%. The authors described a "clinical benefit", as determined by stable disease, pruritis relief, or both in an additional 19 (58%) of the study patients. In common with the study by

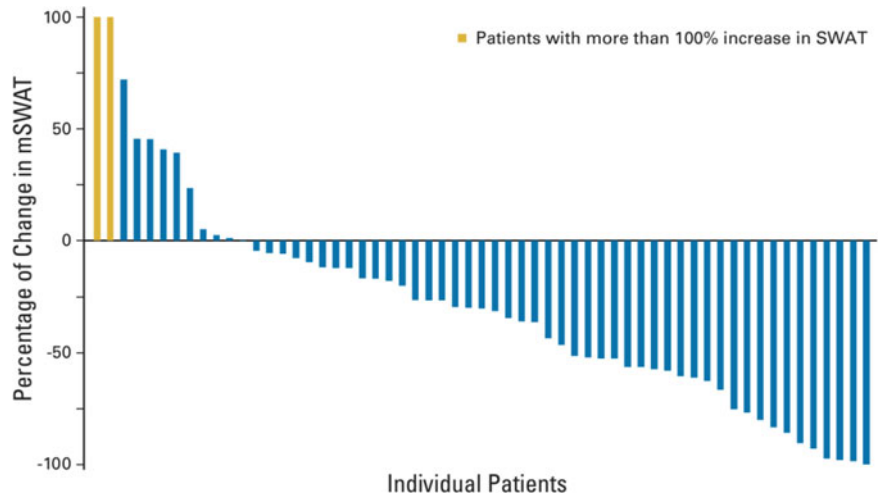

Figure 16.4 Percentage change in mSWAT in the pivotal study of vorinotsat, 47 of 61 patients had a reduced MSWAT score. [Reprinted from Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multi-centre trial of vorinostat in patients with persistent, progressive or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109–15. With permission from American Society of Clinical Oncology.]

Olsen, was the observation that a broad range of clinical CTCL presentations, with responses seen in patients with and without Sézary syndrome and of clinical symptoms such as pruritis. Although statistical comparisons were not possible, it was argued that the intermittent dosing schedule was probably less effective due to a relative, albeit unproven, reduction in drug-induced histone hyperacetylation. The onset of response was similar in tempo to the study by Olsen, as was the time to progression. Those who achieved an objective response were able to maintain it for 9.4–19.6 months (median of 15.1). In both studies, the median duration of treatment was 8 months (range, 1–67).

Romidepsin

The cyclic peptide romidepsin (depsipeptide, FK228, FR901228) is, by contrast to vorinostat, a more specific inhibitor of class-I histone deacetylases. However this does not appear to have been detrimental to clinical effect. To its potential disadvantage, romidepsin is only available as an intravenous formulation. Data is available from two large phase II studies, an international study based at the NCI in the United States [51], the other, European [52]. The treatment schedule was identical across both studies, 14 mg/m^2 intravenously, days 1, 8 and 15 of a 28-day cycle.

The NCI study by Piekarz [51] included patients with both CTCL and PTCL and utilised the RECIST criteria which is typically reserved for studies of non-haematological solid tumours. These criteria stipulate the selection of a limited number of measurable lesions at baseline (minimum 10 mm by calliper), and a partial response requires a 30% reduction in the maximal diameter of all target lesions. The system is perhaps not well suited to the patches and plaques of CTCL, nor to the potential for multiple lesions below the measurable length required for the baseline assessment. Nodal assessment used the Cheson/IWG criteria, in which a partial response requires a 50% reduction in the sum of the product of the diameters of the target lesions. Symptomatic responses, such as improvement in pruritis, were not reported.

The study design was the Simon 2-stage, with the initial cohort of patients not having received more than two systemic therapies. The 44 patients recruited in the second stage of the study had been more heavily treated and in the overall study, patients had received a median of four prior regimens. The severity of disease was similar to the other studies of HDACi in CTCL (Table 16.5). The overall response rate of 34% included four complete remissions. Three of these occurred in the relatively treatment naïve first-stage study. Of the 20 patients that experienced a partial response, 13 had involvement of blood, nodes or viscera. The response duration was 13.7 months for the 24 patients achieving a CR or PR, and 4 months for those with stable disease. As with the vorinostat studies, responses occurred at a median of 8 weeks.

The pivotal 33-centre phase II study of romidepsin by Whittaker et al. [52]. confirmed the observations by Piekarz et al. 96 patients were treated. Response criteria were more rigorous in regard to the skin, using the mSWAT tool (Table 16.3, 16.4) but were more inclusive for lymph nodes, using the RECIST criteria. The authors had an umbrella response score that incorporated all domains of disease (skin, blood and nodes). Nevertheless, they were able to demonstrate an identical response rate of 34%; time-to-response of 8 weeks and response duration of 15 (0–19.8) months. (Fig. 16.5, Table 16.6) This study included assessment of pruritis by a visual scale, as used in the vorinostat studies, and ≥30 mm reduction was seen in 43% of the 65 patients with pruritis, including those without objective disease responses.

Panobinostat

Like vorinostat, panobinostat is also available in oral formulation. Of the studies presented here, the response criteria used in the study for panobinostat were the most comprehensive; however, the criteria used did not require a second confirmation of progression prior withdrawal of patients from the study. In an attempt to adjust for this difference the authors presented multiple post hoc

Table 16.5 Patient characteristics in clinical studies of HDAC inhibitors for cutaneous T-cell lymphoma

	Vorinostat		Romidepsin		Panobinostat
First Author	Olsen [50]	Duvic [41]	Whitakker [52]	Piekarz [51]	Duvic [53]
Total number	74	33	96	71	139
Age; Median (range)	60 (39–83)	67 (26–82)	57 (mean)	57 (28–84)	
CTCL stage (*n, %*)					
IA	0	1 (3)	0	1 (1.4)	36 (25.9)
IB	11 (14.9)	3 (9)	15 (16)	6 (8.5)	
IIA	2 (2.7)	1 (3)	13 (14)	2 (2.8)	
IIB	19 (25.7)	5 (15)	21 (22)	15 (2.1)	70 (50.4)
III	20 (27)	5 (15)	23 (24)	6 (8.5)	
IVA	18 (24.3)	10 (30)	25 (25)	28 (3.9)	0
IVB	4 (5.4)	8 (24)	0	13 (18.3)	33 (23.7)
Number of prior therapies; *n* (range)	3 (1–12)	5 (1–15)	4 (1–11)	4 (0–14)	4 (1–15)
Time from original diagnosis years (range)	2.9 (0.7–27.3)	3.3 (0.2–27.2)	3 (1–26)	–	2.8 (0.1–42)
Sézary syndrome	30 (40.5)	11 (33)	37 (39)	–	38(23.7)
Prior oral bexarotene	71 (95.9)	22 (67)	32 (33)	45 (63.4)	79 (57)
Prior chemotherapy	45 (60.8)	29 (88)	74 (77)	65 (91.5)	–

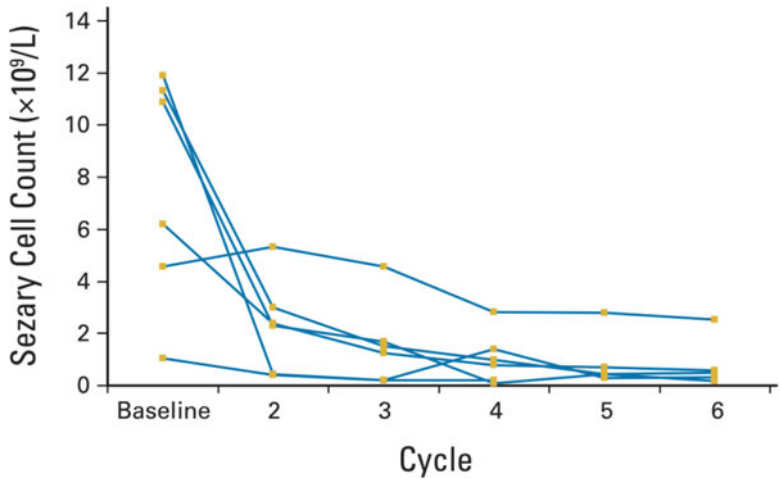

Figure 16.5 Sézary cell counts for 6 of 13 patients with higher blood tumour burden in the study of romidepsin by Whittaker et al. [52] [Reprinted from Whittaker SJ, Demierre M-F, Kim EJ, et al. Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma. Journal of clinical oncology. 2010;28(29):4485–4491. With permission from American Society of Clinical Oncology.]

analyses of patient outcomes, adjusting for the variation in criteria for progression. Patients entering this study were stratified by whether they had received systemic bexarotene as it was hypothesised that the response rate would be less in those who had. That hypothesised difference was not born out in the crude number of responses; however, bexarotene naive patients appeared to enjoy a (statistically insignificant) longer response. Taken together, the lower RR in this study is difficult to place into context of the results reported with vorinostat or romidepsin and at this time it is not possible to determine whether this drug has inferior efficacy (Table 16.6).

Specifically, 139 patients were treated in the study (see Table 16.5). 79 patients (59%) had

Table 16.6 Results from key studies of HDAC inhibitors for CTCL . Abbreviations: TTP: time to progression

	Vorinostat		Romidepsin		Panobinostat
First Author	Olsen [50]	Duvic [41]	Whitakker [52]	Piekarz [51]	Duvic [53]
Total number	74	33	96	71	139
Overall response (%)	29.7	24.2	34	34	17.3
Complete responses; *n* (%)	1 (1.4)	0	6 (6)	4 (7)	2 (1.4)
Median weeks to response (range)	7.9 (4–24.4)	11.9 (3.6–21.9)	8 (3.6–19.2)	8 (4–24)	10.8 (range not available)
Median duration of response; months (range)	NR but estimated ≥6.16 (1–14.7)	15.1 (9.4–19.6)	15 (0–19.8)	13.7 (1–76)	5.6 months in bexarotene exposed and not reached in the bexarotene naïve group.
TTP (months)	4.9 (≥9.8 for stage IIb or greater)	2.82	8 (0–21.7)	15.1 for those responding 5.9 for SD 1.9 for the rest	??
Duration of treatment; median months (range)	8 (4–67)	8 (1–67)	–	4 (1–72)	3 (0.2–29.6)

previously been treated with oral bexarotene [53]. Patients had similar characteristics to those included in other HDACi studies. The overall response rate was 17.3%; 15.2% in those previously exposed to bexarotene and 20% in those who were not. Conversely, the crude response rate was higher in bexarotene-exposed patients with Sézary syndrome (6 of 21, 28.6%) than bexarotene-naïve Sézary patients (2 of 12, 16.7%). The median duration of response in bexarotene-exposed patients was 5.6 months, and was not reached at a median follow up of months (Table 16.6). By applying alternative response criteria similar to those used in the other studies, where confirmation of progression at least 4 weeks after first documentation was required, the adjusted duration of response was reported as 9.2 months in the bexarotene-exposed group. A quarter of the 97 patients with pruritis experienced relief, somewhat less impressive than the results for vorinostat and romidepsin.

The authors attributed the lower response rate of CTCL to panobinostat to two possible causes: insufficient dose and premature withdrawal of patients due to progression that was not confirmed with a period of observation. After re-analysis of the data, only 7 of the 84 patients who progressed during the study period would not have been considered to have progressed if a second confirmation was required. This analysis raised the overall response to 19.4%.Whether attempts to develop panobinostat at higher doses for CTCL will proceed, remains to be seen. Selected phase II dose was based on phase I data from other indications, and experience in Hodgkin lymphoma suggests that higher doses of panobinostat are likely to be more effective. At the time of writing, panobinostat is being developed primarily for use in myeloma in combination with other agents. Overall the clinical findings from studies of HDACi with CTCL are consistent, demonstrating responses in about a third of patients lasting from 6 months to beyond 18 months in a significant minority. This class of agent also offers some symptomatic pruritis relief and appears to be safe.

Romidepsin in PTCL

Presently, no HDACis are approved for the treatment of PTCL. The majority of the clinical data come from the studies of romidepsin. The NCI-led study of romidepsin by Piekarz et al., referred to above, reported the outcomes of patients with PTCL separately from that of CTCL [54]. Response assessment for nodal disease in this and in the other major study in PTCL was by

Table 16.7 Patient characteristics in studies with PTCL. Central reviewa

First Author	Piekarz [54]	Coiffier [55]
Total patient number	47	130
Median Age (range)	59 (27–84)	61 (20–83)
Stage III/IV (%)	45 (96%)	70
Marrow involvement (%)	14 (28%)	36 (28%)
Elevated LDH	26 (55%)	
PTCL NOS	27 (57%)	27 (21%)
Angioimmunoblastic	7 (15%)	27 (21%)
ALCL ALK Positive	2 (4%)	1 (0.7%)
ALCL ALK negative	2 (4%)	21 (16%)
Cutaneous ALCL	2 (4%)	–
Other	4 (8%)	12 (9.2%)
DLBCLa	1(2%)	
Overall response	16 (38%)	38 (39%)b
Complete response	8 (18%)	18 (14)
Median response duration, months (range)	8.9 (2–74)	3 (<1–28+)
Median time to response, months	1.8	1.8
Response duration in complete responders, months (range)	29.4 (3–74)	14 (1.2–26.7+)
Response duration in partial responders, months (range)	5.2 (2–23, ongoing)	17 (0.5–34, ongoing)[a]
Response duration in patients with stable disease	6 (3–12)	Not provided
Median duration of treatment, months (range)	3 (1–57)	1.4 (mean 4.2)

standard lymphoma IWG guidelines [55, 56]. All patients with PTCL had been exposed to systemic chemotherapy and 38% to stem cell transplantation; 40% of patients had previously received radiation. The dose and administration was the same as for patients with CTCL; 14 mg days 1,8 and 15 of a 28-day cycle. Responses are listed in Table 16.7. The overall response rate was 38%, with complete responses observed in eight patients (18%). The time to response was comparable to that seen in CTCL—approximately 2 months. Those with only stable disease ($n=5$) had a median time to progression of 6 (range 3–12) months, with those with PR (9,20%) had a median response of 5.2 months, with some experiencing protracted periods of time on treatment. Overall, the median number of cycles delivered was three (1–57), with 22 of 47 patients receiving less than or equal to two cycles. Toxicities are discussed below.

A multi-centre, international study of 131 patients from 48 centres has recently been completed and reported by Coiffier et al. [55]. The mean age of patients was 59, and a median of 2 prior systemic therapies had been given. 16% of patients had received autologous stem cell transplantation, and all but one systemic chemotherapy. 38% were refractory to the immediate prior therapy. The overall response rate was 30%, which included 21 patients (16%) with a CRu or better. 17% of patients withdrew because of adverse events. The authors noted that the response rate was similarly high in patients who had been refractory to their most recent therapy, reassuring evidence that the HDACis are targeting genuinely novel molecular pathways from those of conventional chemotherapy.

There does not appear to be a particular difference in efficacy across the PTCL subtypes; however, the frequency of specific entities other than PTCL-NOS is low in both trials. The largest subtype of PTCL studied in the romidepsin trials other than PTCL, NOS was angioimmunoblastic lymphoma. While only one of six patients (16%, 95% CI 0.04–64%) with angioimmunoblastic lymphoma responded in the NCI study, [54] 8 of 27 (29%, 95%CI 13.75–50.18%) patients responded in the study by Coiffier et al., similar to the overall response rate for PTCL, NOS. The numbers of patients

Table 16.8 Common toxicities from studies of HDAC inhibitors in CTCL. Approximate ranges are given and rates of toxicities are generally similar between the agents, with the probable exception of diarrhoea which appears to be less common for romidepsin

Most frequent toxicities (all grades)	Diarrhoea ~50% for pan-HDACi and ~10% for romidepsin
	Fatigue ~40%
	Nausea ~20–40%
	Anorexia ~20%
	Thrombocytopenia ~11–50%
	Taste disturbance ~10–50%
Grade III/IV toxicities	Fatigue/aesthenia ~5–7%
	Thrombocytopenia 5–20%
	Anaemia 2–8%
	Neutropenia ~10%
	Sepsis 1–5%

with other subtypes of PTCL are fewer, thus no clear conclusions about differential responses can be made.

Safety and toxicities

As a class of agents, the HDACis share common toxicities, which, with the exception of diarrhoea, do not seem to differ by the HDAC specificity of the agent. Key toxicities in the studies in CTCL are summarised in (Table 16.8). While they appear dose-dependent, they are on the whole across the five studies and the three agents discussed here. In practical use, the most consistent and troublesome toxicities are the mild fatigue and asthenia experienced by approximately half of patients. Similarly common are disorders of taste. Nausea is frequent but more easily treated with standard antiemetics. Thrombocytopenia occurred in up to 40% and was severe (grade III/IV) in up to 20%. The thrombocytopenia of HDACis is rapidly reversible upon withdrawal of the drug and does not appear to relate to cumulative drug exposure. [57] While megakaryocyte numbers increase in response to HDACi, platelet budding is defective, owing to drug-induced phosphorylation of the myosin light chain. [58]

Readers familiar with the treatment of advanced CTCL with systemic chemotherapy will immediately notice the low rates of grade III/IV neutropenia, sepsis or febrile neutropenia associated with the use of HDACis (see Table 16.8). This difference is one of the key advantages of the HDACi, in that they can induce systemic responses without requiring the aggressive prophylaxis against infection or hospitalisation frequently required in patients receiving myelosuppressive combination therapy (especially those with Sézary syndrome).

As consequence of rare episodes of cardiac dysrhythmia in the phase I studies, ECG assessments were systematically performed in the larger HDACi studies. ECG changes have been observed in each of the HDACi discussed here but only rarely have they been of clinical significance. Clinically insignificant QTc prolongation was recorded in 3 patients in the study of vorinostat by Olsen [50] and was not reported in the study by Duvic. [41] T wave flattening was seen in 71% of patients in on the NCI romidepsin study, and ST depression in 9%. Clinically significant QTc prolongation was reported in two patients on the European romidepsin study, which also reported an average prolongation of the QTc interval of 4.6 ms. [51, 59] More detailed study of the initial 42 patients in that trial, which included Holter monitoring in nine patients, showed that the changes in QTc were not associated with elevated cardiac troponin or to changes in left ventricular ejection fraction. [60] One patient had a QTc of >500 ms; however, this occurred in association with abnormal potassium and magnesium levels. Panobinostat and vorinostat also have reports of prolongation of the QTc, rarely as long as 60 ms in the case of panobinostat [61] or 30 ms after a single supratherapeutic dose of vorinostat [62]. QTc prolongation may well be dose and schedule dependent [63]. Despite prolongation of the QTc less than what would usually be considered as significant by regulators, regular ECG monitoring remains a component of the ongoing prospective trials. Replenishment of potassium and magnesium (which may be especially lowered in CTCL) [64] to within normal limits prior to therapy is recommended, particularly prior to administration of intravenous romidepsin. In addition, drugs which

are known to cause prolongation of the QTc should be avoided.

All HDACis should be considered contraindicated in pregnancy. Romidepsin competes with oestrogen for its receptor and therefore, and as is usually the case with other anti-cancer agents, it cannot be assumed that the oral contraceptive pill provides sufficient protection against conception.

Placing HDACi in the overall therapy of T-cell lymphoma, future directions

Based on the evidence and label restrictions, we reserve HDACi for second or subsequent-line therapy of CTCL, and a future role for HDACi in other forms of PTCL seems likely [65]. The possibility of protracted responses makes HDACi an attractive option for patients with advanced and symptomatic CTCL. HDACis are also effective in earlier stages of disease. These agents are generally well tolerated; however, the later onset of response makes HDACi a poor choice if rapid control of symptoms is desired. We frequently find that palliative doses of corticosteroids are needed to ease symptoms in CTCL while a response to the HDACi is anticipated. Combinations with other agents to improve response rates present an attractive concept, with a strong rationale existing for combinations with proteasome inhibitors and other biological therapies [66]. HDACi may also be useful as a chemo- or radiotherapy-sensitising agent. [67] Combination with conventional chemotherapeutics is being tested in Groupe d'Etude des Lymphomes de l'Adulte-led dose escalation study of romidepsin in combination with CHOP chemotherapy (Ro-CHOP, NCT01280526) for PTCL. The results of these trials are eagerly awaited.

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