Romidepsin for cutaneous T-cell lymphoma

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Abstract

Cutaneous T-cell lymphomas (CTCL) are relatively rare lymphomas with an annual incidence of approximately 0.2-0.8/100,000 and comprise a variety of clinical entities; mycosis fungoides (MF) or its leukemic variant Sezary Syndrome (SS) account for the majority of cases. Advanced-stage disease is typically treated with bexarotene (a retinoid), interferon or conventional chemotherapeutic agents but relapses are inevitable. Histone deacetylase inhibitors (HDACi), which modify the epigenome, are an attractive addition to the armamentarium. Based on 2 large phase-II studies, the FDA approved intravenous romidepsin for patients with relapsed/refractory CTCL. Romidepsin provides a subset of patients with an opportunity for prolonged clinical responses with a tolerable side effect profile.
The histone deacetylase inhibitors

The histone deacetylase inhibitors (HDACi) target not only the epigenome via histone modification but also numerous nucleic and cytoplasmic non-histone proteins. They are powerful and selective inducers of cancer cell apoptosis and modifiers of the tumor microenvironment. We refer you to a recent review on this subject. (Figure 1)(1) HDACs are one target for HDAC inhibitors and can be grouped according to their structure and homology to yeast enzymes and share a common mechanism of action in binding a zinc ion critical to HDAC function.

The simplest method of grouping HDAC inhibitors is based on specificity. Class I-specific HDACi include benzamide derivatives (entinostat, mocetinostat) and cyclic tetrapeptides. Romidepsin, isolated from Chromobacterium violaceum [previously called depsipeptide, FK228, FR901228]) is one such bicyclic peptide.(1) The pan-HDAC inhibitors include the hydroxamic acid derivatives (trichostatin A, vorinostat [suberoylanilide hydroxamic acid, SAHA], panobinostat [LBH589]). They were thought to inhibit all of the zinc-dependent HDACs, however recent data suggests relatively reduced effect of the hydroxamates on Class IIa enzymes (HDACs 4, 5, 7 and 9).(2) A key difference between the pan-HDACi and the class 1-specific HDACi is thought to be the inhibition of cytoplasmic HDAC6. It is important to note here that currently, there is very little to suggest that this potential mechanistic difference between the pan-HDACi and the isotype-selective HDACi such as romidepsin effects the response rates (in CTCL at least); response rates to the pan-HDAC inhibitor vorinostat in CTCL are similar to those of romidepsin. There may however be a difference in toxicity profiles.

Preliminary studies of romidepsin

Romidepsin induces apoptosis in many human tumor cell lines and in various xenograft models.(3-5) With respect to CTCL, the most comprehensive pre-clinical studies of romidepsin in a CTCL model have been performed by Piekarz et al. (6) They utilized the human T-cell lymphoma cell line HUT78 to test for sensitivity and molecular response. Romidepsin resulted in histone acetylation, induction of p21 expression, expression of the IL-2 receptor, apoptosis without cell cycle arrest, and induction of the multidrug resistance pump, P-glycoprotein (PGP/ABCB1). PGP was overexpressed in romidepsin-resistance cells, raising the possibility that romidepsin directly induces a mechanism for resistance. (6)

Romidepsin metabolism and pharmacokinetics
Romidepsin is extensively metabolized in vivo, primarily by cytochromes P450 (CYP) 3A4 and to a lesser extent by CYP3A5. In rats 66% of the dose is excreted into the bile, thought to be via PGP/ABCB1. Romidepsin is also likely to be a substrate of the organic anion transporter, OATP1B3, an influx transporter encoded by SLCO1B3 as other cyclic peptides have shown to interact with the same transporter.

Romidepsin is currently only available as an intravenous formulation. In humans, following a 4 hour infusion its half-life is approximately 3.5 hours and over 90% protein bound and metabolized predominantly by CYP3A4 and 66% excreted in bile. The disposition of romidepsin has been shown to follow a polyexponential decline with a linear elimination and has been described by a two-compartment pharmacokinetic (PK) model. No apparent nonlinearity has been reported for romidepsin disposition within the range of 1 – 24.9 mg/m²(7, 8) The PK of romidepsin does not appear to be affected by repeated dosing. The most extensive clinical PK analysis has been performed recently by Woo et al. who PK assessment in 98 patients enrolled in a phase II NCI study (described below) who received 14 mg/m² or 18 mg/m² of romidepsin as a 4-hour infusion on day 1 during their first treatment cycle. Population modeling was performed using a nonlinear mixed effects modeling approach to explore the effects of polymorphic variations in CYP3A4, CYP3A5, SLCO1B3, and PGP/ABCB1, all of which encode genes thought to be involved in romidepsin disposition. There was moderate inter-patient PK variability in clearance (37%) and no statistically significant association was found between romidepsin PK and patient-specific covariates including the polymorphic variants of the cytochrome p450 system tested.(9) The pharmacokinetic pathways involved here will be critical for future drug combination studies, where clinically relevant drug interactions may occur.

Early clinical studies of romidepsin
There have been multiple phase I trials with romidepsin in patients with refractory solid tumors(7, 8) chronic leukemia, myeloma,(10) acute myeloid leukemia(11) and T-cell lymphoma. The maximum-tolerated dose was established at 17-18 mg/m² infused over 4 hours on intermittent dosing schedules. In general, romidepsin was well tolerated and dose-limiting toxicities were constitutional symptoms and thrombocytopenia(7, 8, 10, 11) A phase I trial at the US National Cancer Institute (NCI) demonstrated significant activity in patients with CTCL with three partial responses (PR) observed and one complete response (CR) in a patient with
Trials of romidepsin in CTCL

Romidepsin is an effective agent for the treatment of CTCL. Data is available from two large phase II studies, an international study based at the NCI in the United States, the other, global. The treatment schedule was identical across both studies, 14mg/m² intravenously, days 1,8,15 of a 28 day cycle. The NCI study had a standard Simon 2-stage design, 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 were 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 1). The overall response rate of 34% included four CRs. Of the 20 patients that experienced a PR, thirteen had involvement of blood, nodes or viscera. The response duration was a clinically meaningful 13.7 months for the 24 patients achieving a CR or PR, and four months for those with stable disease (SD). Responses occurred at a median of eight weeks. Symptomatic responses, such as improvement in pruritis, were not reported. In a separate analysis of patients in this trial, Bates et al. evaluated molecular endpoints gathered from a 61 patient subset enrolled (including some PTCL patients included in this study). The biomarker endpoints included histone H3 acetylation and MDR1/ABCB1 gene expression in peripheral blood mononuclear cells (PBMCs) (15, 16); ABCB1 gene expression in tumor biopsy samples; and blood fetal hemoglobin levels (HbF), all of which were increased following romidepsin treatment. With respect to histone acetylation in PBMCs at 24 h, there was a weak to moderate correlation with PK parameters of Cmax and AUClast and inversely associated with drug clearance. Histone acetylation in PBMCs at 24 h was associated with response (p = 0.026) as was the increase in fetal hemoglobin (p = 0.014). The association of response with histone acetylation in PBMCs at 24 h is consistent with a hypothesis that potent HDACi are needed for a critical threshold of drug exposure and durable activity.

The findings of the pivotal 33-centre phase II study of romidepsin by Whittaker et al. were consistent with those of the NCI study. 96 patients were treated. Response criteria were more rigorous in regard to the skin, using the mSWAT tool (see below) and 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 median response duration of 15 (0-19.8) months. This study included assessment of pruritis by a visual scale, as used in the vorinostat studies (below), and ≥30mm reduction was seen in 43% of the 65 patients with pruritis, including those without objective disease responses.

**Safety**

As a class of agents, the HDACi share a similar toxicity profile, however there may be variation by HDACi specificity. Those familiar with the treatment of advanced-stage CTCL with systemic chemotherapy will immediately notice the apparently low rates of grade III/IV neutropenia, sepsis or febrile neutropenia associated with the use of HDAC inhibitors. This ability to induce systemic responses without the need for aggressive prophylaxis against infection or for frequent hospitalisation is key to the attractiveness of this biological agent, when considered against chemotherapy.

Fatigue and asthenia are experienced by many patients, as are disorders of the gastrointestinal system and of taste. Nausea is frequent but generally easily treated with standard antiemetics. Thrombocytopenia occurred in 11-34% and was severe (grade III/IV) in up to 6%. The thrombocytopenia of HDAC inhibitors is rapidly reversible upon withdrawal of the drug nor does it worsen with prolonged romidepsin exposure. (17) While megakaryocytes numbers increase in response to HDACi, platelet budding is defective. (18)

As consequence of rare episodes of cardiac dysrhythmia in the phase I studies, ECG assessments were systematically performed in the phase II studies. 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 2 patients on the global romidepsin study, which also reported an average prolongation of the QTc interval of 4.6 milliseconds. (13) More detailed study of the initial 42 patients in the NCI study, which included Holter monitoring in 9 patients, showed that the changes in QTc were not associated with elevated cardiac troponin or to changes in left ventricular ejection fraction. (19) Other HDACi such as panobinostat and vorinostat also have reports of prolongation of the QTc. QTc prolongation may well be dose and schedule dependent. It is interesting that in a carefully controlled study of vorinostat where supratherapeutic doses were administered, no alteration in QTc
was observed. Nevertheless, as a consequence of the clinical reports, drugs which prolong the QTc should be avoided. Replacement of potassium and magnesium within normal limits prior to therapy is required prior to the romidepsin infusion. Romidepsin competes with oestrogen for its receptor so the oral contraceptive pill must be assumed to be ineffective contraceptive when used alone.

**Romidepsin in CTCL in the context to other HDACi.**

In general, HDACi therapy induces objective responses in CTCL in the order of 25-30% across studies, and each agent is similarly well tolerated. (Table 1) The responses take a median of 8 weeks and up to 2 years to occur, and appear to last somewhere between 6 months and 15 months in responding patients. However if future clinical practice reflects the experience observed in clinical trials, patients will only receive 3 cycles of treatment prior to cessation because of disease progression or drug intolerance. Vorinostat was the first HDACi approved by the FDA, in 2006, for patients with CTCL who had failed two prior systemic therapies. Unfortunately direct comparisons of clinical response between the HDACi are difficult to make, there are no randomized studies comparing the various HDACi in CTCL and the recently published consensus criteria did not exist at the time of design of the various studies discussed here. Nonetheless, romidepsin appears to induce a comparable rate and durability of response to vorinostat (Table 1).

Like vorinostat, *panobinostat* is also available in oral formulation. Panobinostat appears to have both a lower response rate and shorter duration of response and to date has not been registered by the FDA. However these differences may be attributable to the very stringent response and progression criteria used in this study.

**Mechanism of action in T-cell lymphoma – biomarkers and hypotheses**

The accessibility of the skin for biopsy means that CTCL provides an opportunity for the study of the effects of HDACi 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.(21) Studies with the other HDACi in CTCL have given us further insight into possible MOA. With respect to vorinostat cellular localisation of phospho-STAT3 seems to be predictive of response(22, 23). Duvic *et al* also 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. (22) Following a genome-wide loss of function screen Khan and colleagues went on to show that patients whose tumors 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. With respect to panobinostat, Ellis et al provided further support for the anti-angiogenesis hypothesis. (24) 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 downregulation of expression of various transcription factor, cell cycle, immune regulatory and angiogenic genes.

**Placing Romidepsin in the overall therapy of Cutaneous T-cell lymphoma, future directions**

There are no standard algorithms for the management of CTCL suffice to say that in advanced-stage disease, chemotherapy is deferred for as long as possible, with a preference to choose a biological agent as the first systemic therapy. (25) Thus, most treating physicians would choose bexarotene as the first-line agent because of its good toxicity profile and its availability as an oral agent. For most, the next line of therapy will likely to be a choice of interferon, an HDACi or single agent therapy such as oral methotrexate. Pralatrexate is approved for PTCL and has activity in CTCL. The fusion protein, denileukin diftitox is also effective in this group but involves regular IV infusions. Currently, based on the evidence and label restrictions, we reserve HDACi for second or subsequent-line therapy of CTCL. (25) The possibility of protracted responses makes HDACi an attractive option for patients with advanced and symptomatic CTCL. HDACi are also effective in earlier stages of disease and are generally well tolerated. Of note, they have a moderately rapid onset of action and if effective, improvements in skin disease are usually observed within a few weeks of the commencement of therapy.

Once the decision to use an HDACi is made, the clinician will need to choose between vorinostat or romidepsin. One potential advantage of vorinostat is its oral availability. The incidence of thrombocytopenia is generally lower than romidepsin
but this may in part be due to a dose or potency. In the authors experience alterations in renal function appear to be more common with vorinostat. Romidepsin needs to be administered weekly (3 of every 4 weeks) over a four-hour infusion which may make it impractical for some patients. Fatigue and thrombocytopenia are the most common AEs but relatively easily manageable. Although there are no direct comparative trials, the depth and length of responses with romidepsin seem superior.

With respect to the future, combinations with other agents to improve responses and outcomes present an attractive concept, with a strong rationale existing for combinations with proteasome inhibitors, immunomodulatory agents such as lenalidomide, denileukin diftitox and the DNA demethylating agents.
Figure 1: 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. Romidepsin comparatively less effect on HDAC6 compared to the “pan-HDACi”.
# Table: Clinical studies of HDAC inhibitors for cutaneous T-cell lymphoma. Response assessment methods varied considerably across studies.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Vorinostat</th>
<th>Romidepsin</th>
<th>Panobinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsen(26)</td>
<td>Duvic(22)</td>
<td>Whittaker(14)</td>
<td>Piekarz(13)</td>
</tr>
<tr>
<td>Total number</td>
<td>74</td>
<td>33</td>
<td>96</td>
</tr>
<tr>
<td>Age; Median (range)</td>
<td>60 (39-83)</td>
<td>67 (26-82)</td>
<td>57 (mean)</td>
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<td>CTCL stage (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>0 (1-3)</td>
<td>0 (1.4)</td>
<td>36 (25.9)</td>
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<tr>
<td>IB</td>
<td>11 (14.9)</td>
<td>3 (9)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>IIIA</td>
<td>2 (2.7)</td>
<td>1 (3)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>IIB</td>
<td>19 (25.7)</td>
<td>5 (15)</td>
<td>15 (2.1)</td>
</tr>
<tr>
<td>III</td>
<td>20 (27)</td>
<td>5 (15)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>IVIA</td>
<td>18 (24.3)</td>
<td>10 (30)</td>
<td>28 (3.9)</td>
</tr>
<tr>
<td>IVB</td>
<td>4 (5.4)</td>
<td>8 (24)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>Number of prior therapies; n (range)</td>
<td>3 (1-12)</td>
<td>5 (1-15)</td>
<td>4 (1-11)</td>
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<td>Time from original diagnosis years (range)</td>
<td>2.9 (0.7-27.3)</td>
<td>3.3 (0.2-27.2)</td>
<td>3 (1-26)</td>
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<td>Sézary syndrome</td>
<td>30 (40.5)</td>
<td>11 (33)</td>
<td>37 (39)</td>
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<td>Prior oral bexarotene</td>
<td>71 (95.9)</td>
<td>22 (67)</td>
<td>32 (33)</td>
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<tr>
<td>Prior chemotherapy</td>
<td>45 (60.8)</td>
<td>29 (88)</td>
<td>74 (77)</td>
</tr>
<tr>
<td>Overall response (%)</td>
<td>29.7</td>
<td>24.2</td>
<td>34</td>
</tr>
<tr>
<td>Complete responses; n (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Median weeks to response (range)</td>
<td>7.9 (4-24.4)</td>
<td>11.9 (3.6-21.9)</td>
<td>8 (3.6-19.2)</td>
</tr>
<tr>
<td>Median duration of response; months (range)</td>
<td>NR but estimated ≥6.16 (1-14.7)</td>
<td>15.1 (9.4-19.6)</td>
<td>15 (0-19.8)</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>4.9 (≥9.8 for stage Iib or greater)</td>
<td>2.82</td>
<td>8 (0-21.7)</td>
</tr>
<tr>
<td>Duration of treatment; median months (range)</td>
<td>8 (4-67)</td>
<td>8 (1-67)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Notes on response assessments**

**Olsen(26)**
- Skin: mSWAT 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 30mm 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(22)**
- Physician's Global Assessment of Clinical Condition (PGA) 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

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<table>
<thead>
<tr>
<th>Author</th>
<th>Study Details</th>
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| Whittaker (14) | LN: RECIST  
Skin: Composite of SWAT score, and erythroderma scores  
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 30mm reduction for at least 2 cycles considered significant. |
| Piekarz (13) | Skin or Viscera: RECIST  
LN: IWG/Cheson  
Erythroderma: present or absent  
Flow response: present or absent  
PR: either a response in the skin or lymph nodes  
CR: a response in all sites of disease. |
| Duvic (27) | 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: TTP: time to progression; PFS: progression free survival; PGA: Physician’s global assessment of clinical condition; mSWAT: modified severity weighted assessment tool; IWG: international working group; NS: not stated; SPD: sum of perpendicular diameters; VAS: visual analogue scale.
References


Extrinsic apoptosis
Fas, TNF-α, TRAIL upregulation

Intrinsic apoptosis
Upregulation Bid, Bim, Bad
Downregulation Bcl-2, Bcl-Xl, Mcl-1

Inhibition of angiogenesis
Decreased HIF1α and VEGF expression

Oxidative stress
Mitochondrial injury
Inhibition of thioredoxin

Inhibition of thioredoxin

Aggresome-proteasome
Inhibition of alpha-tubulin and misfolded protein response

Cell cycle arrest
Upregulates CDKN1A-p21
Stabilizes p53

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