Romidepsin for Cutaneous T-cell Lymphoma

H. Miles Prince¹,² and Michael Dickinson¹,²

Abstract
Cutaneous T-cell lymphomas (CTCL) are relatively rare lymphomas with an annual incidence of approximately 0.2 to 0.8/100,000 and comprise a variety of clinical entities; mycosis fungoides or its leukemic variant Sezary syndrome 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, which modify the epigenome, are an attractive addition to the armamentarium. On the basis of 2 large phase II studies, the U.S. Food and Drug Administration approved intravenous romidepsin for patients with relapsed and/or refractory CTCL. Romidepsin provides a subset of patients with an opportunity for prolonged clinical responses with a tolerable side effect profile. Clin Cancer Res; 18(13): 1–7. ©2012 AACR.
follow a polyexponential decline with a linear elimination and has been described by a 2-compartment pharmacokinetic (PK) model. No apparent nonlinearity has been reported for romidepsin disposition within the range of 1 to 24.9 mg/m² (7, 8) The PK of romidepsin does not seem to be affected by repeated dosing. The most extensive clinical PK analysis was done recently by Woo and colleagues (9), in which 98 patients were enrolled in a phase II. National Cancer Institute (NCI) study (described below). Patients were tested after they 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 done using a nonlinear mixed effects modeling approach to explore the effects of polymorphic variations in \( \text{CYP3A4, CYP3A5, SLCO1B3, and PGP/ABCB1} \), all of which encode genes thought to be involved in romidepsin disposition. There was moderate interpatient 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, in which 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 to 18 mg/m² infused over 4 hours on day 1 and day 5 of a 21-day cycle and 13.3 mg on days 1, 8, and 15 of a 28-day cycle. 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 NCI showed significant activity in patients with CTCL, with 3 partial responses (PR) observed and one complete response (CR) in a patient with peripheral T-cell lymphoma (PTCL); this study ultimately led to the expanded phase II studies (12).

Trials of Romidepsin in Cutaneous T-Cell Lymphoma

Romidepsin is an effective agent for the treatment of CTCL. Data are available from 2 large phase II studies, an international study based at the NCI in the United States (13), and the other, global (14). The treatment schedule was identical across both studies, 14 mg/m² i.v., days 1, 8, and
15, of a 28-day cycle. The NCI study by Piekarz and colleagues (13) had a standard Simon 2-stage design, with the initial cohort of patients having received not more than 2 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 4 prior regimens. The severity of disease was similar to that shown in the other studies of HDAC inhibitors in CTCL (Tables 1 and 2). The overall response rate of 34% included 4 CRs. Of the 20 patients that experienced a PR, 13 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 4 months for those with stable disease. Responses occurred at a median of 8 weeks. Symptomatic responses, such as improvement in pruritis, were not reported. In a separate analysis of patients in this trial, Bates and colleagues 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 (PBMC; refs. 15, 16); ABCB1 gene expression in tumor biopsy samples; and blood fetal hemoglobin levels, all of which were increased following romidepsin treatment. With respect to histone acetylation in PBMCs at 24 hours, there was a weak-to-moderate correlation with PK parameters of Cmax and AUClast, inversely associated with drug clearance. Histone acetylation in PBMCs at 24 hours was associated with response (P = 0.026), as was the increase in fetal hemoglobin (P = 0.014). The association of response with histone

### Table 1. Patient characteristics and responses in romidepsin studies in CTCL

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Vorinostat</th>
<th>Duvic et al. (22)</th>
<th>Whittaker et al. (14)</th>
<th>Piekarz et al. (13)</th>
<th>Duvic et al. (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Olsen et al. (27)</td>
<td>Duvic et al. (22)</td>
<td>Whittaker et al. (14)</td>
<td>Piekarz et al. (13)</td>
<td>Duvic et al. (28)</td>
</tr>
<tr>
<td>Patients, N</td>
<td>74</td>
<td>33</td>
<td>96</td>
<td>71</td>
<td>139</td>
</tr>
<tr>
<td>Age: median (range)</td>
<td>60 (39–83)</td>
<td>67 (26–82)</td>
<td>57 (mean)</td>
<td>57 (28–84)</td>
<td>61</td>
</tr>
<tr>
<td>CTCL stage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (1.4)</td>
<td>36 (25.9)</td>
</tr>
<tr>
<td>IB</td>
<td>11 (14.9)</td>
<td>3 (9)</td>
<td>15 (16)</td>
<td>6 (8.5)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>2 (2.7)</td>
<td>1 (3)</td>
<td>13 (14)</td>
<td>2 (2.8)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>19 (25.7)</td>
<td>5 (15)</td>
<td>21 (22)</td>
<td>15 (2.1)</td>
<td>70 (50.4)</td>
</tr>
<tr>
<td>III</td>
<td>20 (27)</td>
<td>5 (15)</td>
<td>23 (24)</td>
<td>6 (8.5)</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>18 (24.3)</td>
<td>10 (30)</td>
<td>25 (25)</td>
<td>28 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td>IVB</td>
<td>4 (5.4)</td>
<td>8 (24)</td>
<td>0</td>
<td>13 (18.3)</td>
<td>33 (23.7)</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>
<td>4 (0–14)</td>
<td>4 (1–15)</td>
</tr>
<tr>
<td>Time from original diagnosis in years (range)</td>
<td>2.9 (0.7–27.3)</td>
<td>3.3 (0.2–27.2)</td>
<td>3 (1–26)</td>
<td>NS</td>
<td>2.8 (0.1–42)</td>
</tr>
<tr>
<td>Sézary blood involvement</td>
<td>30 (40.5)</td>
<td>11 (33)</td>
<td>37 (39)</td>
<td>NS</td>
<td>38 (23.7)</td>
</tr>
<tr>
<td>Prior oral bexarotene</td>
<td>71 (95.9)</td>
<td>22 (67)</td>
<td>32 (33)</td>
<td>45 (63.4)</td>
<td>79 (57)</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>45 (60.8)</td>
<td>29 (88)</td>
<td>74 (77)</td>
<td>65 (91.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Percent overall response</td>
<td>29.7</td>
<td>24.2</td>
<td>34</td>
<td>34</td>
<td>17.3</td>
</tr>
<tr>
<td>Complete responses, n (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>6 (6)</td>
<td>4 (7)</td>
<td>2 (1.4)</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>
<td>8 (4–24)</td>
<td>10.8 (range not available)</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>NS but estimated ≥ 6.16 (1–14.7)</td>
<td>15.1 (9.4–19.6)</td>
<td>15 (0–19.8)</td>
<td>13.7 (1–76)</td>
<td>5.6 months in bexarotene exposed and not reached in the bexarotene-naïve group</td>
</tr>
<tr>
<td>TTP, mo</td>
<td>4.9 (≥9.8 for stage IIB or greater)</td>
<td>2.82</td>
<td>8 (0–21.7)</td>
<td>15.1 for those responding, 5.9 for SD, 1.9 for the rest</td>
<td>4.6 (PFS)</td>
</tr>
<tr>
<td>Duration of treatment, median months (range)</td>
<td>8 (4–67)</td>
<td>8 (1–67)</td>
<td>NS</td>
<td>4 (1–72)</td>
<td>3 (0.2–29.6)</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not stated; PFS, progression-free survival; SD, stable disease; TTP, time to progression.
acetylation in PBMCs at 24 hours is consistent with a hypothesis that potent HDAC inhibitors are needed for a critical threshold of drug exposure and durable activity (16). The findings of the pivotal 33-center phase II study of romidepsin by Whittaker and colleagues (14) were consistent with those of the NCI study. A total of 96 patients were treated. Response criteria were more rigorous in the skin, using the modified severity weighted assessment (mSWAT) tool (see below), and were more inclusive for lymph nodes, using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The authors had an umbrella response score that incorporated all domains of disease (skin, blood, and nodes). Nevertheless, they were able to show 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 a 30-mm reduction was seen in 43% of the 65 patients with pruritis, including those without objective disease responses.

Safety
As a class of agents, the HDAC inhibitors share a similar toxicity profile; however, there may be variation by HDAC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Olsen et al. (27)</td>
<td>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 ≥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 antipruritis medications; separate reporting of nodal response, not reported in overall response results: ≥50% reduction in nodal disease or ≥25% reduction in blood tumor burden</td>
</tr>
<tr>
<td>Duvic et al. (22)</td>
<td>PGA; PR, ≥50% improvement in either BSA or skin score with reduction of lymph nodes or blood when involved PD, &gt;25% increase in the number or area of clinically abnormal nodes, or percentage 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</td>
</tr>
<tr>
<td>Whittaker et al. (14)</td>
<td>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 noncutaneous tumor or ≥25% improvement in the sum of the 3 assessments or ≥15% worsening of skin CR, response at all sites Pruritis, VAS with 30-mm reduction for at least 2 cycles considered significant.</td>
</tr>
<tr>
<td>Piekarz et al. (13)</td>
<td>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, response in all sites of disease</td>
</tr>
<tr>
<td>Duvic et al. (28)</td>
<td>Skin, mSWAT, PGA Lymph nodes: Confirmatory CTs were done to exclude disease progression in the nodes at the time of response in the skin PD, ≥25% increase in mSWAT compared with nadir Confirmation of progression not required</td>
</tr>
</tbody>
</table>

NOTE: Response assessment methods varied considerably across studies.

Abbreviations: BSA, body surface area; CT, computer-assisted tomography; IWG, International Working Group; LN, lymph node; PD, progressive disease; PGA, Physician’s Global Assessment of Clinical Condition; SD, stable disease; SPD, sum of perpendicular diameters; VAS, visual analog scale.
inhibitor specificity. Those familiar with the treatment of advanced-stage CTCL with systemic chemotherapy will immediately notice the apparently low rates of grade 3 and 4 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 hospitalization is key to the attractiveness of this biologic 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 antiemetic agents. Thrombocytopenia occurred in 11% to 34% and was severe (grade 3 and 4) in up to 6% of patients. The thrombocytopenia of HDAC inhibitors is rapidly reversible upon withdrawal of the drug, and does not worsen with prolonged romidepsin exposure (17). Although megakaryocyte numbers increase in response to HDAC inhibitors, platelet budding is defective (18).

As a consequence of rare episodes of cardiac dysrhythmia in phase I studies, electrocardiography assessments were systematically done in phase II studies. T-wave flattening was seen in 71% of patients in the NCI romidepsin study and ST segment 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 ms (13). A 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 HDAC inhibitors, 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 and romidepsin, 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 and romidepsin, patients with CTCL who had failed 2 prior systemic therapies with CTCL treated with panobinostat and showed consistent changes in expression in a set of 23 genes, including downregulation of expression of various transcription factors, cell-cycle, immune regulatory, and angiogenic genes.

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Romidepsin in Cutaneous T-cell Lymphoma in Comparison with Other HDAC Inhibitors

In general, HDAC inhibitor therapy induces objective responses in CTCL in the order of 25% to 30% across studies, and each agent is similarly well tolerated (Tables 1 and 2). The responses take a median of 8 weeks and up to 2 years to occur and seem to last somewhere between 6 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 HDAC inhibitor approved by the U.S. Food and Drug Administration (FDA), in 2006, for patients with CTCL who had failed 2 prior systemic therapies. Unfortunately, direct comparisons of clinical response between the HDAC inhibitors are difficult to make, no randomized studies compare the various HDAC inhibitors in CTCL, and the recently published consensus criteria did not exist at the time of design of the various studies discussed here. Nonetheless, romidepsin seems to induce a comparable rate and durability of response to that of vorinostat (Tables 1 and 2).

Like vorinostat, panobinostat is also available in oral formulation. Panobinostat seems 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 the panobinostat 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 HDAC inhibitors on tumor 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 signaling (21). Studies with the other HDAC inhibitors in CTCL have given us further insight into possible mechanisms of action. For vorinostat, cellular localization of phospho-STAT3 seems to be predictive of response (22, 23). Duvic and colleagues also showed that thrombospondin 1, an inhibitor of angiogenesis, is upregulated after exposure to vorinostat, supporting the hypothesis that antiangiogenic effects are important to HDAC inhibitor 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 of HR23B by immunohistochemistry at baseline were more likely to have responsive disease (24). 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 and colleagues provided further support for the antiangiogenesis hypothesis (25). They did serial gene-expression profiling on samples from 10 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 factors, cell-cycle, immune regulatory, and angiogenic genes.

Placing Romidepsin in Overall Cutaneous T-cell Lymphoma Therapy: Future Directions

There are no standard algorithms for the management of CTCL; suffice it to say that in advanced-stage disease, chemotherapy is deferred for as long as possible, with a
preference to choose a biologic agent as the first systemic therapy (26). 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 clinicians, the next line of therapy will likely be a choice of interferon, an HDAC inhibitor, or single-agent therapy, such as oral methotrexate. Pralatrexate is approved for PTCL and has activity in CTCL. The fusion protein denileukin difitox is also effective in this group but requires i.v. infusions. Currently, on the basis of the evidence and label restrictions, we reserve HDAC inhibitors for second- or subsequent-line therapy of CTCL (26). The possibility of protracted responses makes HDAC inhibitors an attractive option for patients with advanced and symptomatic CTCL. HDAC inhibitors 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 HDAC inhibitor is made, the clinician needs to choose between vorinostat or romidepsin. One potential advantage of vorinostat is its oral availability. The incidence of thrombocytopenia is generally lower than that of romidepsin, but this may, in part, be due to a dose or potency. In our experience, alterations in renal function seem to be more common with vorinostat.

Romidepsin needs to be administered weekly (3 of every 4 weeks) over a 4-hour infusion, which may make it impractical for some patients. Fatigue and thrombocytopenia are the most common adverse effects, but they are relatively easy to manage. Although there are no direct comparative trials, the depth and length of responses with romidepsin seem superior.

For 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 and denileukin difitox, and the DNA demethylating agents.

Disclosure of Potential Conflicts of Interest
H.M. Prince received commercial research grants from and is a consultant to Celgene, Merck, and Novartis and received honoraria from Celgene andNovartis. No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions
Conception and design: H.M. Prince, M. Dickinson
Development of methodology: H.M. Prince
Writing, review, and/or revision of the manuscript: H.M. Prince, M. Dickinson
Administrative, technical, or material support: M. Dickinson

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References


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