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REVIEW

Romidepsin for Relapsed and Refractory Cutaneous T-Cell Lymphoma

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Abstract: Romidepsin is a histone deacetylase inhibitor recently approved by the FDA for the treatment of cutaneous T-cell lymphoma. It has led to protracted responses in a significant subset of patients and provides a new treatment option for those refractory to first and second line systemic treatments. Given intravenously, its main toxicities are gastrointestinal as well as haematological. This review discusses the mechanism of action of romidepsin in cutaneous T-cell lymphoma (CTCL), and the clinical trials which provide the basis for FDA approval. We conclude by discussing practical aspects of its administration and give our opinion on how it should be incorporated into the therapeutic armamentarium for patients with refractory CTCL.

Keywords: romidepsin, cutaneous T-cell lymphoma, treatment, novel therapy, biologic agents, depsipeptide

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Introduction

Romidepsin (Istodax, Celgene, Summit NJ) is one of two histone deacetylase inhibitors (HDACi) approved by the FDA for the treatment of relapsed/refractory cutaneous T-cell lymphoma (CTCL). This was based on the demonstration of activity in CTCL in a phase I study and two large phase II studies which confirmed clinical significant activity. Romidepsin is also approved for relapsed/refractory peripheral T cell lymphoma. The HDACi are a drug class which show preclinical activity across a range of malignancies, particularly the hematological malignancies. They have broad biological targets and appear not to act solely through inhibition of the histone deacetylases. In this article we review the mechanisms of action, drug pharmacokinetics and development, safety and clinical response data of romidepsin. We conclude with recommendations for its use and supportive care requirements.

Molecular Targets of the HDACi

The HDACs

The HDAC inhibitors target multiple complex and interconnected cellular pathways. These mechanisms of action have previously been reviewed in detail.[1,2] The conventional wisdom regarding the histone deacetylase inhibitors (HDACi) is that they exert their antineoplastic effect through differential hyperacetylation of histones, consequent changes in the structure of chromatin, and changes to gene expression.[1] Overall, pro-apoptotic genes are preferentially expressed and cancer cells are more sensitive to the sum effects of deacetylase inhibition, and experience preferential apoptosis. The drugs are, therefore, classified according to their target histone deacetylases as well as chemical structure.

HDACs themselves are grouped according to their homology to yeast proteins. The classes of HDAC vary by the localization of the enzyme within the cell as well as by relative distribution in different tissues. Class I enzymes (HDAC 1–3, 8) are found primarily in the nucleus, as is the only member of class IV, HDAC 11. Class IIa includes HDAC 4, 5, 7 and 9 which can shuttle between the nucleus and cytoplasm, and IIb, HDAC 6 and 10, which are predominantly cytoplasmic.[3] Romidepsin, isolated from Chromobacterium violaceum [previously called depsipeptide, FK228, FR901228] is a bicyclic peptide. It is relatively selective for HDACs 1 and 2. By contrast, vorinostat, the other HDACi approved for CTCL, is a "pan-HDACi inhibitor" which targets class IIb HDACs and perhaps less so the class IIa HDACs.[4] A key difference between the pan-HDACi and the class 1-specific HDACi is thought to be the inhibition of HDAC6 by the pan-HDACi. However some preclinical data suggests that romidepsin also leads to partial inhibition of HDAC6.[4] and the potential difference in selectivity may not be clinically significant—it appears not to have affected response rates in clinical trials of T-cell lymphoma. The concept of HDAC selectivity with respect to HDAC6 does however impact the rationale for future combination studies, and there may also be a difference in clinical toxicities.

Apoptosis

The overall effect of HDAC inhibition is induction of pro-apoptotic members of the intrinsic pathway (bak, bax, bim, bmf) and extrinsic (death receptor) pathways (TRAIL, DR4, DR5) and down regulation of the anti-apoptotic members (c-FLIP, BCL-2, BCL-xl, MCL-1 and XIAP).[5–10] The effect of HDACi inhibitors on death receptor pathways may be either through upregulation of expression of death receptors,[11,12] or through expression-independent mechanisms.[13–15]

Cell cycle arrest

Importantly, HDACi induce cell cycle arrest at the G1/S checkpoint, associated with increased $p21^{Waf1}$.[16–20] Arrest at the G2/M checkpoint is observed in normal cell lines,[21] while slippage from this G2/M arrest and subsequent apoptosis in malignant cells may be a mechanism for tumor cell selectivity of these agents.[22] The induction of the cell cycle arrest may occur in either a p53-dependent or p53-independent manner.[23–29]

Other effects of HDACi

HDACi inhibitors induce reactive oxygen species.[30–32] They are anti-angiogenic in particular models of disease (reviewed in Ellis)[33] as well as in tissue samples taken from patients with cutaneous lymphoma[34] and myeloma.[35]

Mechanism of action in cutaneous T-cell lymphoma

The relative importance of each of these cellular effects of the HDACi with respect to anti-tumor function is

Table 1. Clincal characteristics and responses in the two phase II studies of romidepsin.

First author	Whittaker[51]	Piekarz[50]
Total number of patients	96	71
Age; median (range)	57 (mean)	57 (28–84)
CTCL stage (n,%)		
IA	0	1 (1.4)
IB	15 (16)	6 (8.5)
IIA	13 (14)	2 (2.8)
IIB	21 (22)	15 (2.1)
III	23 (24)	6 (8.5)
IVA	25 (25)	28 (3.9)
IVB	0	13 (18.3)
>5% Sézary cells in blood	37 (39)	NS
Prior oral bexarotene	32 (33)	45 (63.4)
Prior chemotherapy	74 (77)	65 (91.5)
Overall response (%)	34	34
Complete responses; n (%)	6 (6)	4 (7)
Median weeks to response (range)	8 (3.6–19.2)	8 (4–24)
Median duration of response; months (range)	15 (0–19.8)	13.7 (1–76)
TTP (months)	8 (0–21.7)	15.1 for those responding 5.9 for SD 1.9 for the rest
Duration of treatment; median months (range)	NS	4 (1–72)

Abbreviations: TTP, time to progression; PFS, progression free survival; NS, not stated; SD, stable disease.

Table 2. Response criteria for the two romidepsin studies.

Whittaker[51]	Lymph nodes: 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 30 mm reduction for at least 2 cycles considered significant
Piekarz[50]	Skin or viscera: RECIST Lymph nodes: 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

Abbreviations: PGA, Physician's global assessment of clinical condition; mSWAT, modified severity weighted assessment tool; IWG, international working group; SPD, sum of perpendicular diameters; VAS, visual analogue scale; CR, Complete response; PR, partial response.

uncertain and is likely to be tumor-type dependent. Signal transducer and activator of transcription 3 (STAT-3) are up regulated in CTCL and may be directly involved in clinical progression.[36] In primary samples from a phase II study of vorinostat, phospho-STAT3 was increased, at baseline, in the cytoplasm and nucleus of malignant lymphocytes. Following treatment, 9 of 11 clinically responding patients had reduced phospho-STAT3 in the nucleus, but an overall increase in the cytoplasmic compartment.[34] This suggested that the HDACi in someway impeded the translocation of activated STAT3 to the nucleus, reducing expression of its target genes. Conversely, work by Shao,[37] suggests that panobinostat, another pan-HDACi active in CTCL, actually reduces overall cellular STAT3.

Duvic et al confirmed preclinical observations regarding the potential antiangiogenic effects of HDACi, demonstrating up regulation of anti-angiogenic thrombospondin-1 in samples taken from patients with CTCL following treatment with vorinostat.[34] Panobinostat down regulates expression of the genes ANGPT1 and GUCY1A3, which are both angiogenic.[38]

Finally, it is likely that the HDAC inhibitors influence the immune milieu through alterations in cytokine profiles. Recent work by Tiffon[39] suggests that IL-10 and IL-2 expression by CTCL cells is decreased in a dose-dependent manner in vitro following exposure to romidepsin and vorinostat. While the IL-2 receptor is expressed on CTCL cells, and an IL-2 autocrine feedback loop is thought to drive CTCL, IL-10 is classically produced by T_{reg} cells and in the setting of CTCL impairs DC maturation and antigen presentation.[39] While clinical data are lacking, these observations support a hypothesis that HDACi modulate the immune derangement observed in CTCL, potentially altering cytokines that drive disease progression and symptoms. Clinical and symptomatic responses to the HDACi may be a product of altered immunology, not merely cell apoptosis. Further support for this hypothesis is the observation that the HDACi are highly active in Hodgkin lymphoma, a disease marked by a cytokine drive for the reactive T_{h2} cells in stroma surrounding Reed-Sternberg cells.[8,40]

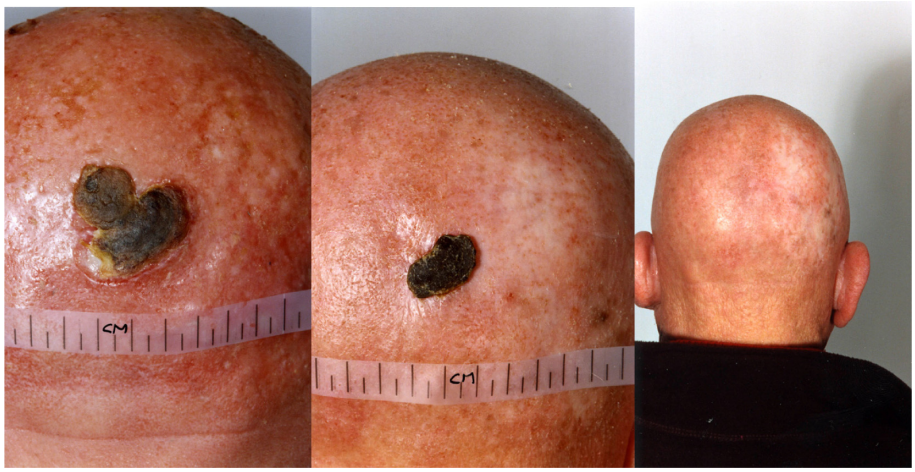

Figure 1. Complete resolution of mycosis fungoides tumor lesion following romidepsin therapy.

Pharmacokinetics of romidepsin

Romidepsin is only available as an intravenous formulation. It is a pro drug that requires intracellular activation though reduction of a disulfide bond.[41] Like other HDAC inhibitors, the active drug interacts with the zinc ion in this histone deacetylase. Romidepsin is extensively metabolized in vivo, primarily by cytochromes (CYP) P450 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. In addition to being a substrate for PGP/ABCB1, romidepsin also induces PGP/ABCB1. In studies of CTCL cell lines PGP was over expressed in romidepsin-resistant cells, suggesting that it may induce a mechanism for its own resistance.[42] Following a four-hour intravenous infusion of romidepsin, the half-life of the drug is 3.5 hours. More than 90% is protein bound and two thirds excreted in the bile. The pharmacokinetics do not appear to be affected by repeated dosing.[43,44] In the large phase II study of romidepsin in T-cell lymphoma, the effects of common polymorphic variations of PGP/ABCB1, CYP3A4, CYP3A5 and SLCO1B3 were studied. While inter-patient clearance of romidepsin varied by as much as 37%, no statistically significant association with the presence of these polymorphisms was found.[45] In a recent study of a one hour infusion time in a multiple myeloma combination study, drug exposure and probably clinical efficacy was shown to be reduced, arguing against clinical use of infusion times less than 4 hours.[46]

Clinically significant drug interactions

Drug-drug interactions need to be considered when administering inhibitors of CYP3A4/CYP3A5. The clinical trial protocols generally excluded co-medication with such drugs so there is limited clinical data. Pharmacodynamic interactions with agents that are known to prolong the QTc interval should also be avoided, as will be discussed below. Specifically excluded supportive care drugs included aprepitant and palanosetron. Ondansetron and granisetron were allowed but the FDA has recently issued a warning about the former suggesting an increased risk of a prolonged QT interval using this agent. Romidepsin competes with estrogen for its receptor so the oral contraceptive pill must be assumed to be less effective in patients on romidepsin.

Early clinical studies

The maximum tolerated dose in phase I studies including patients with a wide variety of malignancies was 17–18 mg/m^2 infused over 4 hours on days 1 and 5 of a 21-day cycle and 13.3 mg on days 1,8 and 15 of a 28 day cycle, with thrombocytopenia and constitutional symptoms the most common dose-limiting toxicities.[43,44,47,48]

Trials of romidepsin in CTCL

Phase II studies in CTCL and peripheral T-cell lymphoma followed early observations of clinical response in the phase 1 study.[49] Data from two large non-randomized studies have led to the registration of

romidepsin for CTCL.[50,51] In both studies, romidepsin was delivered at a dose of 14 mg/m^2 intravenously days 1, 8 and 15 of a 28-day cycle. The NCI study by Piekarz et al had a 2-stage design with the initial cohort of 27 patients having been treated with not more than 2 lines of systemic, therapy, the subsequent 44 having received a median of 4 prior lines of treatment; 4 complete remissions and 20 partial remissions were observed, and the overall response rate was 34%. The median duration of response and time to progression was 13.7 and 15.1 months, respectively, for those patients achieving a CR or PR. Rates of improvement in symptoms such as pruritis were not reported. Those who achieved only stable disease maintained it for a median of 5.9 months. Responses occurred at a median of 8 weeks. Histone acetylation in peripheral blood mononuclear cells at 24 hours was associated with clinical response.[52]

The second, 33-centre phase II study with a single recruitment stage demonstrated similar results.[51] Patients had been treated with a median of 4 prior systemic treatments. Response criteria were more rigorous, formal nodal responses were recorded, and change in pruritis according to a visual analogue scale were recorded. Despite this, a near identical response rate of 34% with a time to response of 8 weeks and median response duration of 15 months was again demonstrated. There was at least a 30% reduction in pruritis score.

Safety and side effects

Gastrointestinal side effects including change in taste, nausea, vomiting and anorexia are commonly seen following romidepsin treatment, occurring in more than half of patients. Nausea is generally easily controlled with standard anti-emetic prophylaxis. Reversible thrombocytopenia, probably a consequence in phosphorylation of the myosin light chain and defective megakaryocytic budding,[53] occurred in 40% of patients in the NCI study and was of grade III/IV severity in 6%. Patients in the international study developed only grade I/II thrombocytopenia, affecting 11%.[51] Grade III/IV neutropenia occurred in 14% of patients and grade I/II fatigue affected approximately a third of patients. Laboratory abnormalities were relatively uncommon, with derangements of AST and ALT occurring in approximately 10%, and relatively mild.

Minor T-wave flattening was seen in 71% of patients in the NCI study, with ST-segment depression in 9%. A more detailed study of the initial 42 patients in the NCI study demonstrated that these changes were not associated with changes in cardiac troponin, clinically significant arrhythmia, or change to ventricular ejection fraction.[54] It is generally accepted that prolongation of the QTc is a class effect of HDACi. Care should be taken to avoid agents that prolong the QTc. Replacement of potassium and magnesium to achieve normal results within normal limits is routine, and can add considerably to the overall time required to administer the drug on a given day in the oncology unit. Entry to the clinical studies of romidepsin precluded patients with known significant or uncontrolled cardiac disease, a fact that must be considered when considering the drug in a community practice.

Comparison with other systemic treatments

Interpretation of clinical studies in cutaneous lymphoma can be difficult as uniform response criteria have only recently been agreed[55] and have not been utilized in the larger clinical studies to date. In addition, large well-structured trials have generally been limited to recently developed agents such as the HDACi and denlileukin diftitox. Randomized comparisons with conventional chemotherapeutic agents are not available. It is not possible to make definitive statements about which of romidepsin and vorinostat are superior. Both appear to have a similar toxicity and safety profile. In the author's experience the incidence of thrombocytopenia is higher with romidepsin whilst taste changes and mild renal dysfunction in higher with vorinostat. The romidepsin trial results showing complete remissions and duration of remissions of many months are compelling. This needs to be weighed up against the inconvenience of a regular 4-hour intravenous infusion. Clearly however, both HDACi have numerous advantages over standard chemotherapy regimens; physicians familiar with systemic chemotherapy for CTCL will generally note a higher initial response rate with such agents albeit with a relatively brief duration of response, and as a consequence of a high rate of cytopenias, a high rate of infection and a potential for hospitalization.[56]

In the absence of standard algorithms for CTCL, it is our practice to reserve the HDACi for patients who have failed at least one initial therapy, in line with the trial data and the FDA label. The possibility of protracted responses with a relatively low risk of infections makes these agents appealing. Most patients who will respond, do so within 8 weeks so a therapeutic trial will usually be short.[56]

The HDACi have given clinicians an entirely new class of agent to treat hematological malignancy and in particular the T-cell lymphomas. We don't yet know precisely why they work in hematological diseases more so than the solid tumors. With a better understanding of what patient or disease factors predict a response to these agents, new more targeted novel agents may be developed. Until then, rational combinations of the HDACi with other novel agents may improve clinical responses and patient outcomes, and warrant exploratory clinical studies. Romidepsin is likely to be an important drug for patients with CTCL, however practical impediments to its delivery will render it a niche agent in the treatment of this rare group of diseases.

Author Contributions

Conceived and designed: MD, HMP. Wrote the first draft of the manuscript: MD, HMP. Contributed to the writing of the manuscript: MD, HMP. Agree with manuscript conclusions: MD, HMP. Jointly developed the structure and arguments for the paper: MD, HMP. Made critical revisions and approved final version: MD, HMP. All authors reviewed and approved of the final manuscript.

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Competing Interests

HMP received commercial research grants from and is a consultant to Merck, Celgene, and Novartis and received honoraria from Novartis. MD has received consulting fees, board membership fees and speaking fees from Celgene and research support from Merck and Novartis.

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