Romidepsin for the Treatment of Peripheral T-Cell Lymphoma

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DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST MAY BE FOUND AT THE END OF THIS ARTICLE.

Key Words. Lymphoma • T cell, peripheral • Romidepsin

ABSTRACT

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of non-Hodgkin lymphomas associated with poor prognosis in most subtypes. Diagnosis of this rare disease by expert hematopathologists improves accuracy of subtyping, and referral to academic or specialty centers is recommended. Many patients, however, will receive treatment in the community, and knowledge of approved agents is key to optimizing therapeutic approaches for all patients. There is no current standard of care for patients with PTCL and no approved therapies for first-line treatment. Although many patients initially respond to induction chemotherapy, responses are often brief, and many patients relapse or become treatment refractory. For patients with relapsed or refractory PTCL, achievement of durable responses is challenging, and there are few treatment options. Romidepsin is a histone deacetylase inhibitor approved by the U.S. Food and Drug Administration for the treatment of patients with cutaneous T-cell lymphoma who have received one prior systemic therapy or more and patients with PTCL who have received one prior therapy or more. Approval of romidepsin for PTCL was based on a pivotal phase II study of patients with relapsed or refractory PTCL (n = 131) that demonstrated an objective response rate of 25% including 15% with complete response; responses lasted a median of >2 years. Long-term responses to romidepsin were achieved in patients regardless of baseline characteristics, including subtype, heavy pretreatment, response to prior therapy, or advanced disease. Common adverse events included hematologic abnormalities, gastrointestinal or asthenic conditions, and infections; romidepsin was not correlated with clinically meaningful QT prolongation or electrocardiogram abnormalities. The Oncologist 2015;20:1084–1091

Implications for Practice: Due to the rarity, severity, and heterogeneous nature of peripheral T-cell lymphoma (PTCL), diagnosis by expert hematopathologists is preferred, and referral to specialty centers is recommended. Many patients, however, will receive treatment in the community, and community oncologists play a key role in the recognition and treatment of PTCL. Knowledge of approved agents is key for optimizing therapeutic approaches. This review provides an overview of PTCL and an in-depth examination of romidepsin, a histone deacetylase inhibitor approved for the treatment of relapsed or refractory PTCL, and highlights difficulties of diagnosis and optimization of treatment modalities for patients with PTCL.

INTRODUCTION

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive T-cell or natural killer (NK) cell forms of non-Hodgkin lymphoma (NHL); nearly all subtypes of PTCL are associated with poor prognosis [1–3]. A number of different PTCL subtype classifications have been proposed previously; the current classification, developed in 2008 by the World Health Organization, is presented in Panel 1 [1]. According to the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, the median age at diagnosis is 62 years, and the most common subtypes diagnosed globally are PTCL–not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL) [2]. The incidence of PTCL subtypes varies geographically, for example, adult T-cell leukemia/lymphoma (ATLL) and NK/T-cell lymphoma (NK/TCL) incidences were higher in Asia than in North America or Europe, and AITL was highest in Europe [2].

T-cell lymphomas have been recognized as distinct from B-cell lymphomas for only the past few decades, and although outcomes are generally poor (with the exception of anaplastic lymphoma kinase-positive [ALK-positive] ALCL), patients with PTCL commonly receive anthracycline-based first-line treatment, based on its reported efficacy for the treatment of B-cell lymphomas [1, 2]. Despite frequent responses to aggressive chemotherapy [4, 5], durable remissions are rare [2]. In the U.S., PTCL accounts for 5%–10% of the estimated 71,850 new cases of NHL diagnosed in 2015 [3, 6]. The incidence of PTCL has been increasing, more than tripling from 1992 to 2009 [7]; however, overall survival (OS) for patients with PTCL did not improve during that time frame,
although several new agents have been approved for the treatment of PTCL since 2009 [7].

**Diagnosis and Staging**

Clinical features and symptoms vary widely across PTCL subtypes, but commonly reported symptoms include enlarged lymph nodes, fatigue, weight loss, rash, and night sweats [8]. Furthermore, a number of organs may be affected, including bone marrow, skin, liver, spleen, and stomach [8]. Diagnosis and PTCL subtype determination are complex and require clinical, histologic, immunophenotypic, molecular, and genetic data [2, 9]; accurate diagnosis requires review by an expert hematopathologist [2, 10]. Initial diagnosis requires a lymph node biopsy for examination of B-, T-, or NK-cell markers. T- or NK/T-cell antigen-positive samples are then further differentiated by lesion morphology and location, genetic testing, and additional immunophenotyping. This process is described in detail in the National Comprehensive Cancer Network (NCCN) guidelines for NHL [10]. Patients are staged using the Ann Arbor staging system, consisting of four stages based on location of disease sites [11]. Stage I disease involves a single lymph node or site, stage II disease involves 2 or more lymph node regions or extranodal sites on the same side of the diaphragm, stage III disease involves lymph node regions on both sides of the diaphragm (with or without extranodal involvement), and stage IV disease has diffuse or disseminated involvement (including involvement in one extranodal site or more, with or without lymph node enlargement) [8, 12]. Computed tomography has been the standard for imaging of PTCL; however, fluorodeoxyglucose positron emission tomography has been used with computed tomography recently for baseline and follow-up examinations [10, 13]. Unfortunately, most patients with PTCL present with advanced-stage disease [2, 11].

**Etiology**

Most subtypes of PTCL have unknown etiology, with the exception of those that are associated with viral infection [2, 14–17]. Human T-lymphotropic virus type 1 (HTLV-1) is known to cause ATLL, and some of the basis of the higher incidence of this subtype in Asia may be related to genetic susceptibility or increased exposure to HTLV-1 [2, 15, 16]. Epstein-Barr virus has also been shown to have an association with extranodal NKTCL, nasal type [17]. ALK-positive ALCL is defined by its expression of ALK protein that may result from oncogenic translocations; however, these translocations do not appear to be sufficient to cause the development of lymphoma [18].

**Prognosis and Treatments**

There is currently no standard of care for the treatment of most PTCL subtypes [10] and no approvals by the U.S. Food and Drug Administration (FDA) for first-line treatment of PTCL. In addition, disease rarity and heterogeneity make treatment selection difficult [1, 2, 10]. Patients with ALK-positive ALCL generally respond positively to anthracycline-based treatments, and NCCN guidelines recommend the CHOP-21 or CHOEP-21 regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone with or without etoposide administered every 3 weeks) in the first line [2, 10]. Because of less favorable results [2, 10, 19], NCCN guidelines recommend clinical trials for first-line therapy in all other subtypes [10]. In the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, >85% of patients with common subtypes of PTCL received anthracycline-containing regimens, resulting in a 5-year OS of 70% for patients with ALK-positive ALCL and 14%–49% for other common PTCL subtypes [2]. Patients with ALK-positive ALCL also tend to be younger (median age: 34 years) than those with other subtypes, and that may contribute to more favorable OS [20]. Prognosis also varies by International Prognostic Index (IPI) score [2], for example, patients with PTCL-NOS had a 5-year OS of 32%: 50% for patients with an IPI score of 0 or 1 versus 11% for those with an IPI score of 4 or 5. Significant risk factors for decreased survival in the IPI include age $>60$ years, stage III–IV disease, the presence of $>1$ extranodal site, a performance status of $>2$, and a serum lactate dehydrogenase level above normal [21].

All patients with PTCL should be considered for consolidation with high-dose therapy and stem cell rescue, with the exception of patients with ALK-positive ALCL and low IPI score who are in remission [10]. Retrospective studies and prospective nonrandomized trials have suggested potential benefits of transplant in first remission; however, many patients fail to achieve remission or are not candidates for transplant [22–28]. Early results from the ongoing Comprehensive Oncology Measures for Peripheral T-Cell Lymphoma

**Panel I: Subtypes of PTCL by WHO 2008 classification [1]**

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Indolent large granular NK-cell lymphoproliferative disorder (provisional)
- ATLL
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma (zob only)
- Primary cutaneous CD30+ T-cell LPDs
- LyP and primary cutaneous ALCL
- Primary cutaneous CD4+ small/medium T-cell lymphoma (provisional)
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)
- Systemic EBV+ T-cell LPD of childhood
- Hydroa vacciniforme-like lymphoma

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; NK, natural killer; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; WHO, World Health Organization.
Treatment (COMPLETE) registry—a national registry of patients with PTCL designed to describe patient characteristics, treatments, and outcomes in a “real world” setting—indicated that <10% of patients with PTCL received a transplant as consolidation of first-line therapy [5]. Second-line treatments include both newer agents and chemotherapy [10]. The rarity of disease and the heterogeneity of subtypes make it difficult to determine optimal therapeutic approaches for all patients [1, 3, 10]. Approved agents for the treatment of relapsed or refractory PTCL include the histone deacetylase (HDAC) inhibitors romidepsin and belinostat, the folate analog pralatrexate, and a CD30-directed antibody-drug conjugate, brentuximab vedotin (currently approved for only the ALC1 subtype) [29–32].

Romidepsin

Romidepsin is an HDAC inhibitor that was initially approved by the FDA in 2009 for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy [29]. It was then approved in 2011 for the treatment of PTCL in patients who have received at least one prior therapy [29]. Romidepsin is recommended by the NCCN as second-line and subsequent therapy in patients, regardless of intention to proceed to high-dose therapy or stem cell transplant (SCT) [10].

Mechanism of Action

HDACs catalyze the removal of acetyl groups from both histones and nonhistone proteins, repressing transcription of DNA and affecting the function of various cellular proteins [33, 34]. Aberrant HDAC activity has been noted during transformation to a cancerous state [35, 36]. As anticancer agents, HDAC inhibitors work through several mechanisms, including activation of cell death, cellular differentiation, and inhibition of angiogenesis [35, 36]. A number of different HDAC inhibitors, which differ in specificity, structure, and potency, have been investigated as anticancer agents [34–37]. Romidepsin is a structurally unique, potent, bicyclic class 1 HDAC inhibitor [33, 37–39] and currently is the only HDAC inhibitor approved for the treatment of both CTCL and PTCL. Combinations of various HDAC inhibitors with other anticancer agents are being explored to target malignant cells through multiple pathways (see ClinicalTrials.gov).

Efficacy and Safety of Romidepsin in Patients With PTCL

The National Cancer Institute (NCI) conducted a phase I trial that examined the maximum tolerated dose (MTD) of romidepsin in 37 patients with various cancers [40]. Dose-limiting toxicities included fatigue, transient cytopenias, nausea and vomiting. Prophylactic use of antiemetics was initiated at doses of $\geq 3.5$ mg/m$^2$ [40], and reversible electrocardiogram (ECG) changes without evidence of myocardial damage were also seen at doses of $\geq 3.5$ mg/m$^2$ [40]. Notably, changes in ECG parameters, including corrected QT (QTc) intervals, have been shown to be associated with some antiemetics [41, 42]. The MTD of romidepsin was determined to be 17.8 mg/m$^2$ as a 4-hour infusion on days 1 and 5 of a 21-day cycle [40]. Of the four patients enrolled with T-cell lymphoma, three with CTCL each achieved a partial response (PR) and one with PTCL achieved a complete response (CR) to romidepsin [43]. A separate phase I study enrolling patients with advanced cancer demonstrated similar results on a different dosing schedule, with a reported MTD of 13.3 mg/m$^2$ as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle [44].

The NCI also conducted a phase II trial of romidepsin in patients with relapsed or refractory PTCL or CTCL [45, 46]. Forty-seven patients with various subtypes of PTCL were enrolled. The first 2 patients initiated treatment at 18 mg/m$^2$ as a 4-hour infusion on days 1 and 5 of a 21-day cycle (based on the MTD in the NCI phase I study [40]), but the schedule was changed for improved tolerability, and patients received romidepsin at 14 mg/m$^2$ as a 4-hour infusion on days 1, 8, and 15 of 28-day cycles [44, 46]. Patients were heavily pretreated (median of 3 prior therapies) and most had advanced disease (23% and 72% with stage III and IV disease, respectively; 55% with elevated lactate dehydrogenase and 30% with bone marrow disease involvement) [46]. The objective response rate (ORR; PR plus CR) assessed by investigators in 45 evaluable patients was 38%, including 8 patients (18%) with a CR (Table 1). Responses were seen across all major PTCL subtypes, in 6 of 18 patients with prior SCT [46], and regardless of patient age [47].

A larger ($n = 131$), pivotal phase II study of romidepsin in patients with relapsed or refractory PTCL who had $\geq 1$ prior systemic therapy was also conducted [48]. Patients received romidepsin at 14 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle for up to 6 cycles; those who experienced stable disease, PR, or confirmed or unconfirmed CR (CR/CRu) and tolerated the drug could continue beyond 6 cycles [48]. Responses were assessed in a rigorous two-step process by an independent review committee (IRC) consisting of a radiologic assessment followed by a broader clinical assessment by expert radiologists and hematologic oncologists [48]. Patients were heavily pretreated (median of 2 prior therapies), and most had advanced disease (70% with stage III or IV disease, 76% with IPI score $\geq 2$) [48]. For the 130 patients with histologically confirmed PTCL, the ORR as assessed by the IRC was 25%, including 19 patients (15%) with CR/CRu (Table 1) [48, 49]. There were no significant differences in response rates based on patient subgroups, including major PTCL subtype, sex, age, IPI score, number or type of prior therapies, or response to last prior therapy [48]. Most responses were noted at the first response assessment following 2 treatment cycles, whereas the median time to CR/CRu was >3.7 months [48]. The median duration of response was 28 months (median follow-up: 22.3 months) [49], and of the 19 patients who achieved CR/CRu, 10 experienced responses lasting $\geq 12$ months. In an updated analysis, the longest response is ongoing at $\geq 56$ months in a patient withAITL [50]. None of the baseline characteristics examined (e.g., heavy pretreatment, response to prior therapy, advanced disease) precluded long-term response to romidepsin [49]. Achievement of CR/CRu was associated with prolonged progression-free survival (PFS) and OS compared with all other outcomes [49]. Of the 33 patients with best response of stable disease, 23 (70%) had stabilization for $\geq 90$ days (SD90) [51], and patients with best response of PR or SD90 had similar PFS and OS [49].

The most common adverse events (AEs) reported in phase II studies of romidepsin for the treatment of relapsed or refractory PTCL included gastrointestinal disturbances,
asthenic conditions, infections (all types pooled), and transient cytopenias (Table 2) [29, 46, 48, 52]. The majority of AEs were mild to moderate in severity, and most infections were unrelated to romidepsin treatment. Discontinuation due to AEs (most commonly thrombocytopenia, anemia, or infection) occurred in 19% and 28% of patients in the pivotal and NCI studies, respectively [29]. Grade ≥3 AEs and discontinuations were highest during the first 2 cycles of treatment [49, 52], and extended therapy did not affect the reported safety profile, including no evidence of cumulative cardiac toxicity [46, 49].

The hydroxamate pan-HDAC inhibitor belinostat was also recently approved for the treatment of patients with relapsed or refractory PTCL [30]. Belinostat 1,000 mg/m² is given as a 30-minute intravenous infusion on days 1–5 of a 21-day cycle. In a phase II study (n = 129; 120 evaluable for efficacy), belinostat demonstrated a 26% ORR, including 11% with CR and a median duration of response of 8 months. The most common grade 3–4 AEs were anemia (11%), thrombocytopenia (7%), dyspnea (6%), and fatigue (5%). Discontinuation due to AEs occurred in 19% of patients, most commonly due to anemia, febrile neutropenia, fatigue, or multiple organ failure. Of note, no studies to date have compared the safety and efficacy of romidepsin and belinostat in patients with relapsed or refractory PTCL.

Trials examining the combination of romidepsin with conventional chemotherapy regimens or newer agents are ongoing. In a single-arm, phase Ib/II study, patients with biopsy-proven PTCL were to receive eight 28-day cycles of CHOP (cyclophosphamide 750 mg/m² on day 1, doxorubicin 50 mg/m² on day 1, vincristine 1.4 mg/m² on day 1, and prednisone 40 mg/m² on days 1–5) with varying doses of romidepsin [8, 10, or 12 mg/m² on days 1 and 8] [53]. Based on the results of this MTD study, the recommended dosing schedule of romidepsin for the phase II portion was 12 mg/m² on days 1 and 8 of each cycle. Grade ≥3 hematologic AEs occurred in the majority of patients, and the most common nonhematologic toxicities were gastrointestinal, respiratory, or general conditions [53]. Among 35 evaluable patients (phase Ib and II combined), the ORR was 69%, including 51% with CR. At the median follow-up of 30 months, the estimated PFS and OS were 41% and 71%, respectively. A phase III trial of CHOP with or without romidepsin is under way (RoCHOP study, NCT01796002) with planned enrollment of 420 adult patients and a primary endpoint of PFS [54]. Romidepsin is also currently under investigation for patients with PTCL and other hematologic malignancies in various combinations, including with the anthracyline liposomal doxorubicin (NCT01902225), CHOP chemotherapy (NCT02223208), ICE chemotherapy (ifosfamide, carboplatin, and etoposide; NCT01590732), aurora A kinase inhibitor alisertib (NCT01897012), proteasome inhibitors bortezomib (NCT00963274) or carfilzomib (NCT01738594), the IMiD immunomodulatory drug lenalidomide (NCT01742793, NCT01755975, NCT02232516), lenalidomide and carfilzomib (NCT02341014), nucleoside analogs CC-486 (oral azacitidine; NCT01998035) and gemcitabine (NCT01822886), gemcitabine-based regimens (GDP [gemcitabine, dexamethasone, and cisplatin], NCT01846390; GemOdx [gemcitabine, oxaliplatin, and dexamethasone], NCT02181218), or the folate analog pralatrexate (NCT01947140).

Cardiac Safety of Romidepsin

ECG changes have been described with several HDAC inhibitors including romidepsin [55–63], and a class effect has been suggested previously [35, 56, 64]. In the phase I NCI study of romidepsin, reversible grade 1 T-wave flattening, grade 2 T-wave inversions with ST-segment depression, and asymptomatic arrhythmias were observed on post-treatment ECGs, with no evidence of myocardial damage [40]. One patient treated above the MTD had an episode of atrial fibrillation that was dose limiting and did not recur when the patient was retreated at the MTD. Routine cardiac monitoring and electrolyte supplementation were incorporated into the clinical program, and patients with known significant cardiac abnormalities were excluded from phase II studies [48, 64]. In the pivotal study of romidepsin for relapsed or refractory PTCL, there were no significant changes in QT intervals during the first 4 cycles of treatment, and ECG abnormalities were reported in 8 patients (6%), including 3 patients with QTc prolongation (1 grade 3); none of these patients had concurrent symptoms of syncope or other cardiac AEs at the time of reported ECG abnormality [48]. In the phase II NCI study, asymptomatic T-wave changes were reported in more than half of the patients, although all changes were reported as AEs regardless of clinical significance [45, 46]. Intensive cardiac monitoring of patients from the NCI study showed no association with romidepsin and myocardial damage or impaired cardiac function [64]. An updated ECG analysis of the NCI study showed that most patients required electrolyte supplementation and concluded that when

### Table 1. Efficacy of romidepsin in phase II trials in relapsed or refractory PTCL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pivotal trial [48, 49] (n = 130)</th>
<th>NCI trial [46] (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>33 (25)</td>
<td>17 (38)</td>
</tr>
<tr>
<td>CR*</td>
<td>19 (15)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (11)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>SD</td>
<td>33 (25)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>SD90</td>
<td>23 (18)</td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

*Median follow-up of 22.3 months.

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Electrolyte levels are kept within the normal range, data support the cardiac safety of romidepsin. Results from a thorough postmarketing cardiac study in patients with various advanced malignancies (n = 29) showed that despite the use of QT-prolonging antiemetics, romidepsin did not significantly prolong QTc, even at supratherapeutic dose levels. Romidepsin is associated with transient heart rate increases (without evidence of increased arrhythmia) that should be taken into account during patient selection. Reported increases in QTc with romidepsin treatment are likely exaggerated by increased heart rate and concomitant antiemetic administration.

Changes in ECG parameters, including QTc intervals, are a class effect of antiemetic 5-hydroxytryptamine 3 (5-HT3) receptor agonists, such as ondansetron, which was commonly used with romidepsin. Antiemetic selection occurs locally but may be determined by institutional standards. Granisetron has been reported to have a lesser effect than ondansetron on QT intervals and next-generation 5-HT3 receptor agonist palonosetron was shown to not significantly increase QT intervals. Romidepsin should be used with caution and in the setting of appropriate cardiac monitoring in patients with a history of significant cardiovascular disease or those taking antiarrhythmic medicines or medicinal products that lead to significant QT prolongation.

Administration of Romidepsin

Approved romidepsin dosing is the same as that tested in phase II studies: 14 mg/m² as a 4-hour intravenous infusion on days 1, 8, and 15 of a 28-day cycle as long as the patient continues to benefit from and tolerate the drug. Dose reduction to 10 mg/m² or interruption may be necessary in the event of hematologic or nonhematologic toxicities (except alopecia). In the event of grade 2 nonhematologic toxicity, treatment should be delayed until toxicity returns to grade 1 or baseline. The resumed dose should be reduced to 10 mg/m² in the event of recurring grade 3 or 4 toxicity. If grade 3 or 4 toxicity resumes following dose reduction, use of romidepsin should be discontinued. Hematologic abnormalities such as neutropenia, thrombocytopenia, and lymphopenia are dose-limiting toxicities.

An updated ECG analysis of the NCI study showed that most patients required electrolyte supplementation and concluded that when electrolyte levels are kept within the normal range, data support the cardiac safety of romidepsin.

Table 2. Most common adverse events (≥10%) in the pivotal trial and corresponding incidence in the National Cancer Institute study of romidepsin for the treatment of relapsed or refractory PTCL

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pivotal trial (n = 131) [29]</th>
<th>NCI trial (n = 47) [29]a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades, n (%)</td>
<td>Grade 3/4, n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>77 (59)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Infections (all types pooled)b</td>
<td>72 (55) [48]</td>
<td>25 (19) [48]</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>72 (55)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>53 (41)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>51 (39)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (36)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>46 (35)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39 (30)</td>
<td>28 (20)</td>
</tr>
<tr>
<td>Constipation</td>
<td>39 (30)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>37 (28)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>32 (24)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>27 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>23 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18 (14)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (13)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16 (12)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Chills</td>
<td>14 (11)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14 (11)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13 (10)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>13 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>13 (10)</td>
<td>0</td>
</tr>
</tbody>
</table>

aThe NCI study reported all abnormalities as adverse events, regardless of clinical significance [47].
bNone of the individual preferred term events in the infections system organ class were reported in ≥10% in either study.

Abbreviations: NCI, National Cancer Institute; NR, not reported; PTCL, peripheral T-cell lymphoma.
as thrombocytopenia and neutropenia are common in patients with PTCL [48], and based on clinical trial results with romidepsin, patients should be monitored for thrombocytopenia, neutropenia, lymphopenia, and anemia during treatment [29]. If grade 3 or 4 thrombocytopenia or neutropenia occurs with romidepsin, treatment should be delayed until platelet count returns to $\geq 75 \times 10^9$/L and/or absolute neutrophil count returns to $\geq 1.5 \times 10^9$/L or baseline, at which point romidepsin can be restarted at 14 mg/m$^2$ [29]. In the event of thrombocytopenia requiring platelet transfusion or grade 4 febrile neutropenia, romidepsin should be delayed until grade $\leq 1$ or baseline, followed by permanent romidepsin dose reduction to 10 mg/m$^2$ [29]. Patients with advanced-stage disease and/or a high tumor burden should also be monitored for tumor lysis syndrome, which was reported in 2% of patients with stage III or IV PTCL [29].

Because of the incidence of nausea and vomiting, prophylactic antiemetics are recommended for use in all patients prior to each romidepsin dose. The need for electrolyte supplementation is common for patients with T-cell lymphoma [65, 70]; hypomagnesemia and hypokalemia may be associated with ECG abnormalities [64, 67] and are known risk factors for cardiac arrhythmia and sudden cardiac death [71–74]. Potassium and magnesium should be monitored throughout treatment and be in the normal range before romidepsin administration [29], which can be achieved through electrolyte supplementation (Table 3). Because some patients in the pivotal study of romidepsin for relapsed or refractory PTCL received prolonged treatment, the protocol was amended to allow for maintenance dosing of 2 romidepsin doses per cycle for patients who received $\geq 12$ treatment cycles and 1 dose per cycle for patients who received $\geq 24$ treatment cycles and had received 2 doses per cycle for $\geq 6$ treatment cycles [49].

Patients should be monitored for toxicity related to increased romidepsin exposure (may require dose reduction) when coadministered with strong CYP3A4 inhibitors, and coadministration with potent CYP3A4 inducers should be avoided (Table 3) [29]. Prothrombin time and international normalized ratio should be monitored more frequently in patients who are concurrently receiving romidepsin and warfarin (or derivatives), and caution should be exercised when concurrently administering romidepsin and P-glycoprotein inhibitors because of the potential to increase the concentration of romidepsin (Table 3) [29]. Patients with moderate or severe hepatic impairment or end-stage renal disease should also be treated with caution because the effects on romidepsin pharmacokinetics are unknown [29].

Patients should be monitored for toxicity related to increased romidepsin exposure (may require dose reduction) when coadministered with strong CYP3A4 inhibitors, and coadministration with potent CYP3A4 inducers should be avoided.

### Role of Expert Hematopathologists and Specialty Treatment Centers in the Management of PTCL

Among patients with common subtypes of PTCL referred to NCCN comprehensive cancer centers ($n = 131$), diagnostic concordance with the referring center occurred in only 44% of patients [75]. Among 1,314 cases reviewed by expert hematopathologists in the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study, $< 90\%$ were confirmed as PTCL or NK TCL [2]. Accurate diagnosis of PTCL involves correlation of many pieces of patient information, including clinical, histologic, immunophenotypic, molecular, and genetic data [2, 9]. Even among expert hematopathologists, consensus subtype diagnosis ranged from 97% for ALK-positive ALCL to 66% for primary cutaneous ALCL [2]. Individual site-entered data ($n = 119$) from the COMPLETE registry reviewed by expert hematopathologists showed that errors in recording or interpretation of biomarker data were common during the diagnostic workup of PTCL, with only 11% of entries containing no errors [76]. Recent strides in molecular profiling may help improve the diagnosis and prognostication of major PTCL subtypes [77]. In addition, development of new diagnostic markers has resulted in an amended diagnosis of some cases of PTCL-NOS to AITL [78], and other cases of PTCL-NOS have been shown to have genomic aberrations resembling ATLL [79, 80]. At this time, expert hematopathologist review is strongly recommended to provide optimal care to patients with PTCL as early as possible.

PTCL is heterogeneous and relatively rare compared with other cancers that may be seen by oncologists [6]. Despite inducing durable responses with manageable toxicity in patients with PTCL, many oncologists are not aware of the role of romidepsin in the PTCL treatment paradigm. In a survey of 100 U.S.-based medical oncologists that assessed prescribing experiences with newer oncologic drugs, only 31% were very confident about prescribing romidepsin for T-cell
lymphoma [81]. In addition to the agents approved for treatment of PTCL (romidepsin, belinostat, pralatrexate, and brentuximab vedotin for the ALC1 subtype), NCCN treatment guidelines for nearly all subtypes (ALK-positive ALC1 being the exception) recommend that patients be considered for inclusion in clinical trials [10, 29, 31, 32]. Consequently, referral to specialty treatment centers is recommended.

CONCLUSION

For patients with PTCL, varying clinical features, heterogeneity of subtypes, issues with subtype diagnosis, and limited guidelines make determination of optimal therapeutic approaches difficult. Treatment of this rare disease in a community setting requires that clinicians empower themselves with information on disease, diagnosis, and available therapies. Romidepsin has demonstrated durable responses and long-term tolerability in patients with relapsed/ or refractory PTCL and is recommended by the NCCN for use in the second and subsequent lines for patients with PTCL, regardless of eligibility for high-dose therapy or SCT.

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