

Romidepsin Induces Durable Responses in Relapsed/Refractory PTCL

Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30:631-636.

Peripheral T-cell lymphomas (PTCL) are a rare, heterogeneous group of mature, post-thymic T-cell lymphomas that primarily affect older adults.¹ Patients commonly present with advanced, systemic symptoms and disseminated disease.² PTCL is often aggressive, demonstrating a poorer response to therapy than aggressive B-cell lymphomas.³ An exception is the subset of patients with anaplastic lymphoma kinase-1 (ALK-1)-positive anaplastic large-cell lymphoma (ALCL), in whom outcomes are more favorable.⁴

No standard therapy has been established for PTCL. Anthracycline-containing chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP-like regimens are used, although they often fail to induce adequate, durable responses.⁴ Moreover, no single agent is currently approved for the initial treatment of PTCL.

Until recently, no therapies were approved for the treatment of relapsed or refractory PTCL. However, the past several years have seen the introduction of several new agents for the treatment of PTCL. In 2009, the antifolate pralatrexate (Folotyn, Allos) gained accelerated approval from the US Food and Drug Administration (FDA) based on results of a single-arm, phase II trial. In 109 patients with relapsed or refractory PTCL, pralatrexate was associated with an objective response rate (ORR) of 29%, including 11% complete responses or unconfirmed complete responses (CR/CRu) and a median duration of response (DOR) of 10.1 months.⁵

Romidepsin (Istodax, Celgene) is a potent, selective histone deacetylase (HDAC) inhibitor that has been shown to increase transcription of tumor suppressor genes, inhibit cell growth, promote cell cycle regulation, and induce apoptosis.^{6,7} In 2009, romidepsin was approved for the treatment of cutaneous T-cell lymphoma (CTCL) following at least 1 prior systemic therapy. The antitumor activity of romidepsin in patients with recurrent or refractory PTCL was first demonstrated in phase I and II trials conducted by the National Cancer Institute (NCI).^{8,9} Among 45 evaluable patients in the phase II study, romidepsin was associated with an ORR of 38%, including 18% CRs.⁹

Coiffier and colleagues undertook a second phase II study to further evaluate the efficacy and safety of romidepsin in patients with relapsed or refractory PTCL after prior systemic therapy. This pivotal study led to the 2011 FDA approval of romidepsin for the treatment of patients with PTCL who have received at least 1 prior therapy. Findings from the study were previously presented at the 2010 Annual Meeting of the American Society of Hematology¹⁰ and the 2011 Annual Meeting of the American Society of Clinical Oncology.¹¹ They were recently published in the *Journal of Clinical Oncology*.¹²

Study Description

This study was a prospective, single-arm, multicenter, phase II trial conducted at 48 centers in the United States, Europe, and Australia. The study enrolled 130 patients with PTCL histologically confirmed by central review. All patients were required to have received at least 1 prior systemic therapy; patients with ALK-1-positive ALCL were required to have relapsed following autologous stem cell transplantation (ASCT). Additional inclusion criteria included measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hematologic and organ function. Exclusion criteria included nontransformed mycosis fungoides or Sézary syndrome, CNS involvement, and cardiac abnormalities. Patients could not have received any cancer therapy within 4 weeks of study entry (6 weeks for nitrosoureas), and were required to meet minimum serum potassium and magnesium levels, due to risks of hypokalemia and hypomagnesemia with romidepsin.

The treatment consisted of romidepsin administered at 14 mg/m² as a 4-hour intravenous infusion on days 1, 8, and 15 every 28 days for up to 6 cycles. Patients could extend therapy until disease progression or until another event that would prompt discontinuation.

The median age of eligible patients was 61 years (range, 20–83 years), 68% were male, and 89% were white. The most common histologic subtype was PTCL-not otherwise specified (NOS; 53%), followed by angio-

immunoblastic T-cell lymphoma (21%), ALK-1–negative ALCL (16%), enteropathy-type T-cell lymphoma (5%), and subcutaneous panniculitis-like T-cell lymphoma (2%). ALK-1–positive ALCL; cutaneous gamma/delta T-cell lymphoma; extranodal NK/T-cell lymphoma, nasal type; and transformed mycosis fungoides were identified in 1 patient each. One additional patient enrolled but was excluded from efficacy analysis due to a diagnosis of diffuse B-cell lymphoma.

Disease was advanced in the majority of patients; 70% had stage III or IV disease, 76% had an International Prognostic Index (IPI) of at least 2, and 28% had bone marrow involvement. The median time since PTCL diagnosis was 1.3 years (range, 0.2–17 years), and patients had received a median of 2 prior systemic therapies (range, 1–8). Nearly all patients had received chemotherapy (most commonly CHOP), 15% had received monoclonal antibody therapy, and 11% had received other types of immunotherapy, including denileukin diftitox and interferon. Twenty-one patients (16%) had received prior ASCT, and 38% of patients were refractory to their last therapy.

Outcome

Based on the Independent Review Committee analysis, romidepsin was associated with an ORR of 25%, including 15% CR/CRu. Another 25% of patients maintained stable disease (SD), with 70% of patients remaining in SD for at least 90 days. The investigators' assessments yielded similar efficacy outcomes, with ORR and CR/CRu rates of 29% and 16%, respectively. The median duration of response was 17 months overall and among patients who achieved CR/CRu, with the longest response ongoing at 34 months. After a median follow-up of 13 months, 90% of patients in CR/CRu were still in remission. The median time to any response was 1.8 months, and the median time to CR/CRu was 3.7 months.

Subgroup analyses revealed similar response rates across the more common PTCL subtypes, including in PTCL-NOS (29%), AITL (30%), and ALK-1–negative ALCL (25%). CR/CRu rates in these subgroups were 15%, 19%, and 19%, respectively. Although responses were not observed in other subtypes, patient numbers were insufficient to draw conclusions. In the 49 patients refractory to their last therapy, the response rate was 29% (18% CR/CRu). The investigators reported no significant differences in response rates based on patient characteristics, disease characteristics, or prior treatment history, including the number of prior therapies and the type of regimens used.

The median PFS was 4 months among all patients, 18 months among patients with CR/CRu, 7 months among patients with PR, and 6 months among patients

with stable disease. Moreover, 70% of patients with SD responses to romidepsin were also associated with improvements in ECOG performance status among the 82 patients with a baseline performance status of 1–2. Among these patients, performance status improvements were observed in 83% of patients with CR/CRu, 60% of patients with PR, and 52% of patients with SD.

Safety

Romidepsin was generally well tolerated, with adverse events largely manageable and expected based on prior experience with romidepsin and other HDAC inhibitors. The most common adverse events were nausea (59%), infections (55%), fatigue (55%), thrombocytopenia (41%), vomiting (39%), diarrhea (36%), and pyrexia (35%). The most frequent grade 3/4 adverse events were thrombocytopenia (24%), neutropenia (20%), infection (19%), and anemia (11%). Cardiac studies revealed T-wave abnormalities in patients receiving romidepsin, although these were not associated with cardiac adverse events, such as syncope or clinically significant QT intervals.

Although more than half of patients developed an infection, 37% of infections were not considered to be drug-related; the incidence of drug-related infections was 18% (6% grade 3/4). Moreover, the incidence of any single type of infection was less than 10%, with the most common infections being upper respiratory tract infections (8%), urinary tract infections (7%), pneumonia (6%), and sepsis (5%). Factors associated with an increased risk of grade 3/4 infection were use of prior monoclonal antibody therapy (30% vs 14% among other patients) and bone marrow involvement (30% vs 12% among other patients). Of the 17 patients who developed pneumonia or sepsis, 6 patients had progressive disease.

Nearly half of patients (47%) required at least 1 dose interruption, most often due to thrombocytopenia (18%), infections (12%), and neutropenia (11%). Adverse events resulted in dose reductions from 14 mg/m² to 10 mg/m² in 14 patients (11%), most commonly due to thrombocytopenia (3%), which generally recovered between cycles. Adverse events resulted in discontinuation of romidepsin in 19% of patients (10% attributed to drug-related adverse events). The most common adverse events that led to therapy discontinuation were thrombocytopenia and pneumonia, although no single adverse event resulted in treatment discontinuation in more than 2% of patients.

Eight patients (6%) died within 30 days of their last dose of romidepsin, although the last dose had been administered at least 3 weeks prior in 7 of 8 patients. Causes of death included progressive disease only (3 patients), infection, or an event that occurred during infection. There was 1 death considered to be possibly

treatment-related, in a patient with sepsis and progressive disease who had received 2 doses of romidepsin.

Clinical Relevance

This pivotal trial—the largest trial to be conducted in this patient population—demonstrated significant activity with romidepsin in patients with relapsed or refractory PTCL, a population with no established standard of care. Single-agent romidepsin induced objective responses in 25% of patients (15% with CR/CRu). The median response duration of durable remissions was 17 months. Moreover, many patients with stable disease on romidepsin appeared to have clinical benefit, with 70% remaining progression-free for at least 90 days. Responses to romidepsin were observed across patient subgroups and occurred regardless of treatment history, including the number of prior therapies, the response to prior therapy, or the prior use of ASCT.

Adverse events were similar to those previously reported with romidepsin and other HDAC inhibitors, and included gastrointestinal effects, hematologic toxicities, infection, and fatigue. The most common drug-related adverse events were grade 1/2 nausea and vomiting. Moreover, although hematologic abnormalities were common, they led to treatment discontinuation in only 4% of patients.

Summary

The findings of this trial indicate that romidepsin fills an unmet need for an effective treatment option in patients with relapsed or refractory PTCL. The authors suggested that

romidepsin should be further evaluated in additional settings, including in previously untreated patients and in combination with other agents.

References

1. López-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. *Ann Oncol*. 1998;8:849-855.
2. Rodriguez-Abreu D, Filho VB, Zucca E. Peripheral T-cell lymphomas, unspecified (or not otherwise specified): a review. *Hematol Oncol*. 2008;26:8-20.
3. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997;89:3909-3918.
4. Vose J, Armitage J, Weisenburger D, et al. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26:4124-4130.
5. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol*. 2011;29:1182-1189.
6. Rasheed W, Bishton M, Johnstone RW, Prince HM. Histone deacetylase inhibitors in lymphoma and solid malignancies. *Expert Rev Anticancer Ther*. 2008;8:413-432.
7. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov*. 2006;5:769-784.
8. Piekarz RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. *Blood*. 2001;98:2865-2868.
9. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood*. 2011;117:5827-5834.
10. Coiffier B, Pro B, Prince HM, et al. Final results from a pivotal, multicenter, international, open-label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy. Presented at the 53rd Annual Meeting of the American Society of Hematology, December 4-7, 2010; Orlando, Florida. Abstract 114.
11. Horwitz SM, Coiffier B, Foss FM, et al. Complete responses (CR/CRu) on a phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL). Program and abstracts of the 2011 Annual Meeting of the American Society of Clinical Oncology; June 3-7, 2011; Chicago, Illinois. Abstract 8033.
12. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30:631-636.

Commentary

Romidepsin for Previously Treated Patients With Peripheral or Aggressive T-Cell Lymphomas

Steven M. Horwitz, MD

Medical Oncologist
Memorial Sloan-Kettering
Cancer Center
New York, New York

Address correspondence to:

Steven M. Horwitz, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; E-mail: horwitzs@mskcc.org.

This pivotal phase II study of romidepsin (Istodax, Celgene) led to the approval of this agent for previously treated patients with peripheral or aggressive T-cell lymphomas.¹ The initial study identifying romidepsin as a possibly useful agent for peripheral T-cell lymphomas was from the National Cancer Institute (NCI), which conducted a phase I trial that identified several surprisingly good responses in patients with cutaneous or peripheral T-cell lymphoma.^{2,3} The NCI then conducted a larger, multicenter study examining a broader experience in T-cell lymphoma that included patients with cutaneous and peripheral T-cell lymphomas at various stages of their disease.⁴ This study found that there was reasonable activity of romidepsin in a wide range of patients with both cutaneous and peripheral T-cell lymphomas. One cohort of that study focusing on peripheral T-cell lymphoma (n=47) found an overall response rate (ORR) of 38% (95% confidence interval, 24–53%) and a median duration of overall response of 8.9 months (range, 2–74 months).⁵

The article recently published in the *Journal of Clinical Oncology* described the final results of the pivotal phase II trial in 131 patients with peripheral T-cell lymphoma.¹ This trial defined the activity of romidepsin in these patients. The ORR in this study was 25%. The primary endpoint, complete response rate (as mandated by the US Food and Drug Administration), was 15%.

Clinical Use of Romidepsin

In patients with relapsed peripheral T-cell lymphoma, romidepsin has been used most often to try to control disease in the relapse setting. In this study, the 25% response rate was coupled with a median duration of response of approximately 17 months. Among patients who achieved a complete response, the median duration of response was not met by the time the study was reported. One conclusion of this study is that romidepsin can be an effective treatment for a significant minority of patients beyond first-line therapy. When we look at results of single agents in relapsed T-cell lymphomas, achieving some response and controlling the disease for 6–12 months is likely of clinical benefit to the patient. These results suggest that romidepsin clearly has use in the palliative setting.

The second most common use of romidepsin in patients with relapsed T-cell lymphoma is to aid in the transition to a more definite or curative therapy, which would be allogeneic stem cell transplant. In that situation, a greater degree of response is desired. While romidepsin did result in a complete response in some patients, its main value in this setting is when patients are not responding well enough to other agents to permit transplant, or when the process of identifying a donor and arranging the transplant is on a longer time frame, as sometimes occurs. In this setting, a therapy that can be given for a prolonged period of time without cumulative toxicity is desired. Most patients with T-cell lymphoma will relapse from initial therapy, and this use of romidepsin is an important addition to our therapeutic options.

Future Directions

Ideally, the response rate of 25% seen in the trial would be higher. Efforts to improve this result are leading to several lines of clinical investigation. One approach would be to combine romidepsin with other agents to produce a stronger upfront combination regimen that might lead to a higher initial cure rate. There is a phase I study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) that is examining romidepsin in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), to try to create a more robust upfront regimen.⁶ Romidepsin is also being examined in combination with other nonchemotherapy regimens or other single-agent chemotherapies to try to build a better combination regimen.

Another potential use of romidepsin could be as a maintenance therapy. Romidepsin has been associated with a moderate response rate, reasonable tolerability, and reasonable durability. Trials employing this approach after treatments such as CHOP or upfront autotransplant are being developed, and represent another way to try to incorporate novel agents into our current therapies for T-cell lymphomas.

References

1. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol*. 2012;30:631-636.
2. Sandor V, Bakke S, Robey RW, et al. Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. *Clin Cancer Res*. 2002;8:718-728.
3. Piekarz RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. *Blood*. 2001;98:2865-2868.
4. Piekarz R, Frye R, Wright J, et al. Update of the NCI multiinstitutional phase II trial of romidepsin, FK228, for patients with cutaneous or peripheral T-cell lymphoma. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2007;25(suppl 18): Abstract 8027.
5. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood*. 2011;117:5827-5834.
6. ClinicalTrials.gov. A Study of Escalating Doses of Romidepsin in Association With CHOP in the Treatment of Peripheral T-Cell Lymphomas (Ro-CHOP). <http://clinicaltrials.gov/ct2/show/NCT01280526>. Identifier: NCT01280526.