Received: 1 August 2016 | Revised: 14 March 2017 | Accepted: 20 March 2017

DOI: 10.1002/hon.2421

WILEY

CASE REPORT

Complete remission with romidepsin in a patient with T-cell acute lymphoblastic leukemia refractory to induction hyper-CVAD

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Abstract

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) are neoplasms that originate from T-cell precursors. Outcomes in adult patients with T-ALL/LBL remain unsatisfactory; early relapse following intensive induction chemotherapy is a concern, and patients with relapsed or refractory disease have a poor prognosis. Romidepsin is a potent, class 1 selective histone deacetylase inhibitor approved for the treatment of patients with peripheral T-cell lymphoma who have had ≥1 prior therapy and patients with cutaneous T-cell lymphoma who have had ≥1 prior systemic therapy. Here, we report the case of an adult patient with T-ALL refractory to induction hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD). Treatment with romidepsin was initiated, and romidepsin in combination with hyper-CVAD resulted in complete remission, with mild tumor lysis syndrome as the only detectable additional toxicity. The patient eventually underwent allogeneic stem cell transplant while in first complete remission. Prior studies have shown that romidepsin is capable of inducing durable responses with manageable toxicities in patients with mature T-cell lymphomas. This case study describes the successful use of romidepsin in combination with hyper-CVAD in an adult patient with refractory T-ALL and highlights the activity of romidepsin in the T-cell lineage. The potential of romidepsin-containing regimens in patients with T-ALL/LBL deserves further study.

KEYWORDS

chemotherapy, early T-cell precursor acute lymphoblastic leukemia/lymphoma, histone deacetylase inhibitor, romidepsin, T-cell acute lymphoblastic leukemia, T-cell lymphoblastic lymphoma

1 | INTRODUCTION

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) originate from lymphoblasts committed to the T-cell lineage and are classified by the World Health Organization as a single entity, regardless of leukemic or lymphoma disease manifestations.[1] T-ALL and T-LBL have similar lymphoblast morphology and immunophenotype but differ in gene expression profile, clinical prognostic factors, and responses to treatment—although T-ALL-like regimens have shown effectiveness in patients with T-LBL.[1-6] Outcomes for adult patients with T-ALL/LBL remain unsatisfactory, and patients with relapsed or refractory disease face a particularly poor prognosis with low overall survival rates.[5,7-11] It is acknowledged that new agents are needed for treatment of refractory/relapsed T-ALL/LBL. Efforts are underway to identify immunohistochemistry and gene profile markers that identify patients at higher risk of refractory or relapsed disease. Once high-risk patients are identified, novel induction treatments can be studied to potentially improve outcomes.

We report the case of an adult female patient with T-ALL that progressed twice during her first cycle of hyper-CVAD (cyclophosphamide + vincristine + doxorubicin + dexamethasone). Flow cytometry results indicated that the disease may have been early T-cell precursor (ETP)–ALL/LBL with additional high-risk features.[12] Although several regimens have been reported, the optimal reinduction therapy for relapsed or refractory T-ALL or T-LBL remains unclear.[5,7,11] Radiation was added for the first progression, and romidepsin was added for

the second lymph node progression, which occurred outside of the radiation field. Romidepsin, which is approved for treatment of relapsed/refractory T-cell non-Hodgkin lymphoma (peripheral T-cell lymphoma [PTCL] and cutaneous T-cell lymphoma [CTCL]) in the United States,[13] was chosen because it was unlikely to exacerbate her mucositis due to chemoradiotherapy, to significantly worsen her neutropenia, or add end-organ toxicity. Upon rapid progression after induction with a standard adult induction regimen, the patient consented to salvage therapy with hyper-CVAD with the addition of romidepsin.

2 | PATIENT DATA AND METHODS

A 38-year-old previously healthy woman presented to an outside hospital on October 6, 2014, with T-ALL. Her workup was completed at the Colorado Blood Cancer Institute, and she consented to chemotherapy with hyper-CVAD and all subsequent salvage chemoradiotherapy, using institutional review board–approved consent forms for treatment. The patient provided prior written consent for the anonymous use of her data and was treated in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and this institution's institutional review board.

The workup was initiated at an outside hospital on October 7, 2014, and consisted of contrast enhanced computed tomography (CT) of the neck, chest, abdomen, and pelvis, with a bone marrow biopsy. An echocardiogram and diagnostic lumbar puncture with prophylactic intrathecal methotrexate were initiated after she was transferred to the Colorado Blood Cancer Institute for management. The peripheral blood white-blood cell count was 43 000/μL (40% circulating T-cell lymphoblasts), hemoglobin 6.9 g/dL, and platelets 108 000/μL. Her bone marrow biopsy confirmed lymphoblastic leukemia with 100% cellularity and 73% T-cell lymphoblasts. The T-cell lymphoblasts were positive for CyCD3, CD7, CD13, CD38, CD45, CD45RA, and CD117, with partial expression of CD2, CD123, and HLA-DR, and were negative for CD1a, CD3, CD4, CD8, CD11b, CD14, CD15, CD16, CD33, CD34, CD45RO, CD56, CD84, CD10, and myeloperoxidase. TdT was negative by flow cytometry, but positive by immunohistochemistry. Taken together, the immunohistochemistry and flow cytometry was most consistent with pre-T-ALL.[14] Our case is suggestive of ETP-ALL/LBL in the current World Health Organization nomenclature; however, CD5 was not characterized and definitive determination was not possible.[12,14,15] ETP-ALL/LBL neoplasms originate from thymocytes that do not express CD1a or CD8, have weak expression of CD5, and express 1 or more stem cell (CD117) or myeloid markers.[14,15]

The lymphoblast karyotype revealed 46, XX with trisomy 4 and del X (q13). Total-body CT showed a 1.7 × 2.2 cm left neck lymph node mass with additional lymph nodes throughout the left and right neck.

The patient began hyper-CVAD cycle 1A on October 11, 2014, and her peripheral blood blasts resolved. Clinically, the left neck lymph node mass initially decreased in size by over 50%. By day 7 of hyper-CVAD cycle 1A, the left neck lymph nodes grew, exceeding their initial size, and were treated with 4 radiation fractions to the involved left neck lymph nodes. The left neck lymph node mass responded to the radiation. During this radiation treatment of the left neck, the T-ALL lymph nodes in the right neck progressed by contrast-enhanced CT performed on October 28, 2014, "mid cycle" of hyper-CVAD cycle 1A. The patient was neutropenic due her recent chemoradiotherapy at the time of the second progression. Romidepsin 14 mg/m^2 as a 4-hour infusion was initiated on days 11 and 18 of hyper-CVAD cycle 1A to treat the progression of T-ALL within the right neck. Twenty-four hours after the first dose of romidepsin, the patient experienced mild orthostatic hypotension, increased phosphate and potassium levels, decreased calcium levels, and negative blood culture results. The clinical picture was most consistent with mild tumor lysis syndrome and was treated with intravenous hydration and urine alkalization.

After hyper-CVAD cycle 1A with romidepsin, a positron emission tomography (PET)/CT showed minimal areas of ^{18}F-fluorodeoxyglucose uptake in the involved lymph nodes in the left and right neck. The patient was readmitted on November 22, 2014, to undergo cycle 1B of hyper-CVAD with planned supplemental romidepsin on days 11 and 18. An abscess developed after radiation within the necrotic left neck lymph node mass and was drained before the high-dose methotrexate and cytarabine of hyper-CVAD cycle 1B. The drained material was sterile and contained no viable T-ALL. The patient completed a 3-week course of clindamycin and ertapenem, without recurrence of the abscess. The patient entered a complete remission (CR) by the end of cycle 1B of romidepsin-supplemented hyper-CVAD with no morphological T-ALL in the bone marrow biopsy or positron emission tomography PET/CT evidence of disease. As is standard in our program for patients with primary refractory disease, the patient underwent an allogeneic (HLA-identical sister) peripheral blood hematopoietic stem cell transplant (PB-HSCT) in first CR with fludarabine/total body irradiation (400 cGy) on January 3, 2015. The patient remains in CR with mild chronic graft-versus-host disease 22 months after the transplant.

3 | DISCUSSION

Outcomes for patients with relapsed or refractory T-ALL/LBL remain unsatisfactory, with poor overall survival rates.[5,7-11] In a Medical Research Council/Eastern Cooperative Oncology Group study, 123 of 334 patients (37%) relapsed after induction therapy; 27 of these 123 patients went on to receive allogeneic stem cell transplant, and 8 survived at a median of 5.2 years.[8] Hyper-CVAD with or without nelarabine has been used to treat adults with T-ALL/LBL, but the risk of early relapse is a concern.[6,7,16] Our patient progressed after cycle 1A of hyper-CVAD—a "standard" adult T-ALL/LBL induction.[6,7]

Although a definitive determination was not possible without the characterization of CD5, the CD1a$^-$ and CD8$^-$ T-cell blasts within the bone marrow and a blast count of >20% suggest that our patient may have had ETP-ALL/LBL.[12,14,15] The limited available data seem to indicate that patients with ETP-ALL/LBL may fare even worse than those with mature T-ALL/LBL.[12] The CR rate for hyper-CVAD-based or augmented BFM chemotherapy in patients with ETP-ALL/LBL is only 73% vs 91% for non-ETP-ALL/LBL, with a median overall survival of only 20 months.

Romidepsin is a histone deacetylase (HDAC) inhibitor approved for the treatment of patients with PTCL who have received ≥1 prior

therapy and for patients with CTCL who have had ≥1 prior systemic therapy.[13] Although the underlying mechanisms remain unclear, HDAC inhibitors in general, and romidepsin in particular, have demonstrated activity in mature T-cell lymphomas.[17-20] In the 2 pivotal phase 2 trials that led to approvals in each respective indication (PTCL and CTCL), romidepsin induced durable responses with manageable toxicity.[18-20] Furthermore, manageable myelosuppression has been reported with romidepsin added to standard cell cycle–active chemotherapy, suggesting that it could be combined with our patient's treatments for primary refractory disease (dose-intense induction chemotherapy and radiation).[21] In the case presented here, one reason for the selection of romidepsin was the potential for minimal toxicity when added to chemotherapy for the primary refractory T-ALL. Romidepsin given to our patient with T-ALL on days 11 and 18 appeared to enhance the effectiveness of hyper-CVAD and radiation, resulting in a CR, allowing for allogeneic PB-HSCT, and with mild tumor lysis syndrome as the only detected additional toxicity.

Romidepsin may increase the effectiveness of frontline chemotherapy in patients with T-ALL/LBL, potentially decreasing the number of patients with primary refractory disease and ultimately leading to improved overall survival. The response in this patient with T-ALL indicates that although approved for use in more mature T-cell lymphomas, romidepsin may have activity in more immature T-cell malignancies. Although there are relatively little preclinical and clinical data on the activity of romidepsin in T-ALL/LBL, the combination of romidepsin with oral azacitidine (hypomethylating agent) in an early-phase clinical trial resulted in CR in a patient with relapsed/refractory T-ALL.[22-25] In our program, patients with high-risk T-cell lymphomas who have CR with romidepsin-containing initial or salvage chemotherapy have a low relapse rate after allogeneic transplant (data available on request). Romidepsin-containing chemotherapy regimens deserve further study in this high-risk population.

ACKNOWLEDGEMENTS

The authors take full responsibility for the content of this manuscript, but thank William Ho, PhD (MediTech Media, Ltd), for providing medical editorial assistance. Financial support for medical editorial assistance was provided by Celgene Corporation.

CONFLICT OF INTEREST

Mark W. Brunvand has been a consultant for Celgene Corporation. John Carson has nothing to declare.

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How to cite this article: Brunvand MW, Carson J. Complete remission with romidepsin in a patient with T-cell acute lymphoblastic leukemia refractory to induction hyper-CVAD. *Hematological Oncology*. 2018;36:340–343. https://doi.org/10.1002/hon.2421