A phase I study of romidepsin and ifosfamide, carboplatin, etoposide for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma

The survival outcome of patients with peripheral T-cell lymphoma (PTCL) who experience relapse or progression following first-line treatment is generally very poor.[1] It can improve for patients who are able to receive stem cell transplantation (SCT), particularly if remission prior to transplant is achieved.[2] Currently, there is no one standard salvage therapy for PTCL, except brentuximab vedotin (BV) for patients with anaplastic large cell lymphoma (ALCL), and either combination chemotherapies or targeted agent monotherapies, such as romidepsin, are commonly used.[3-5] Such combinations offer the potential of improving outcomes for patients with PTCL by increasing complete remission (CR) rates and durability of remissions.[6] Here we report an open-label single institute phase I study I clinical trial combining romidepsin and ifosfamide, carboplatin, etoposide (ICE) in patients with relapsed/refractory PTCL. (This trial is registered at *clinicaltrials.gov identifier: 01590732.*)

The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the institutional review boards of the centers involved. The primary objective of the study was to assess the safety profile of this combination and to determine the maximum tolerated dose (MTD).

Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and adequate renal and hepatic function were included in the study. Patients with central nervous involvement were excluded.

Romidepsin was given intravenously (IV) on days 1 and 4 at 8 mg/m^2 (dose level 1), 10 mg/m^2 (level 2), or 12 mg/m^2 (level 3). ICE consisted of: ifosfamide IV 5 g/m^2 on day 1, mesna IV 5 g/m^2 on day 1, carboplatin IV with an area under the curve (AUC) of 5 on day 1, and etoposide IV 100 mg/m^2 on days 1-3. A Bayesian method was used to assign patients to each dose level. Cycles were repeated every 14 days with growth factor support, for up to 6 cycles. Toxicity was graded using the Common Terminology Criteria for Adverse Events v.4.0. Dose limiting toxicity (DLT) was only assessed during cycle 1, and defined as any grade 3 or 4 non-hematologic toxicity attributed to romidepsin that could not be controlled or prevented by supportive care, or as grade 4 neutropenia or thrombocytopenia lasting longer than 14 days. The MTD was defined as the dose at which 20% of the patients experienced a DLT.

Eighteen patients were enrolled between February 2013 and April 2016. Baseline characteristics are shown in Table 1. Two patients were enrolled at dose level 1 of romidepsin (8 mg/m^2), 15 at dose level 2 (10 mg/m^2), and one at dose level 3 (12 mg/m^2). The number of total cycles provided for each level was 7, 39, and 1, respectively. Median number of cycles per patient was 3 (range, 1-5 cycles), and the median time interval between subsequent cycles was 21 days (range, 14-33 days).

Median time on study was two months (range, 1-13 months). Reasons for study discontinuation were: indication for SCT in 12 patients, lack of response in one, consent withdrawal in one, and toxicity in 4 patients (allergy, ototoxicity, thrombocytopenia, and renal insufficiency).

Two patients were enrolled on dose level 1, and no dose-limiting toxicities (DLTs) were observed. Two patients were enrolled at dose level 2, as per study design, and no DLTs were observed. One patient was enrolled at dose level 3; this patient had a persistent grade 4 thrombocytopenia which was considered a DLT. Thus, as per study design, dose level 2 was expanded to include an additional 13 patients. Of these, one patient had an episode of acute renal failure, which was considered a DLT, but per study design the cohort expansion was continued and no additional DLT was observed. So, dose level 2 was identified as MTD for future phase II studies.

Among all enrolled patients, the most common (>10% of patients) grade 3-4 toxicities were thrombocytopenia (83%), anemia (50%), neutropenia (44%), fatigue (33%), nausea/vomiting (33%), infections (28%), dyspnea (17%), and transaminitis (11%).

Fifteen out of 18 treated patients were evaluable for response: 3 patients stopped treatment after 1 cycle before first response evaluation because of toxicity (allergy, ototoxicity, and thrombocytopenia).

Overall response rate (ORR) was 93%: 12 (80%)

Table 1. Patients' baseline characteristics.

Patients (n=18)	Number (%), median [range]
Median time from diagnosis (months)	5 [2-45]
Age (years)	59 [21-68]
Age > 65 years	3 (17)
Males	13 (72)
Diagnosis: PTCL-NOS	7 (39)
AITL	7 (39)
ALK+ ALCL	1 (5.5)
ALK- ALCL	1 (5.5)
NK/TCL	1 (5.5)
HSTL	1 (5.5)
Ann Arbor stage I	0 (0)
II	3 (17)
III	5 (28)
IV	10 (55)
Previous regimens (n)	1 [1-2]
Previous regimen > 1	1 (5.5)
Latest regimen: CHOP	8 (44.5)
CHOEP	5 (28)
EPOCH	1 (5.5)
HCVAD/ MTX-Ara-C	2 (11)
BV-CHP	2 (11)
Previous autologous SCT	1 (5.5)
Previous radiation therapy	1 (5.5)
Response to previous regimen: CR	4 (22)
PR	0 (0)
SD	2 (11)
PD	12 (67)
Relapsed < 6 months	16 (89)

n: number; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; NK/TCL: natural killer T-cell lymphoma; HSTL: hepatosplenic gamma-delta T-cell lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; HCVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate, cytarabine; BV-CHP: brentuximab, cyclophosphamide, doxorubicin, prednisone; SCT: stem cell transplant; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

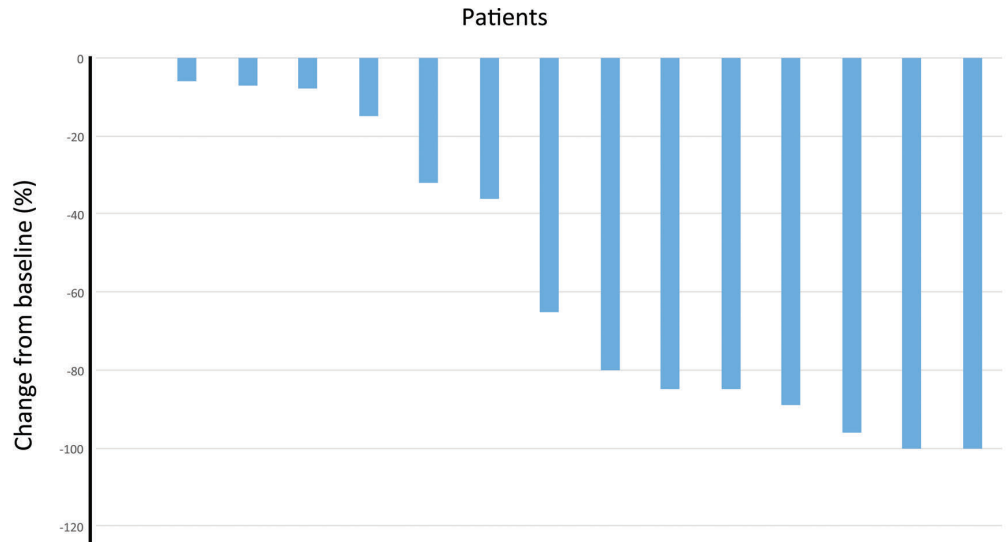

Figure 1. Waterfall plot showing best response in tumor size from baseline.

patients achieved CR and 2 patients achieved (13%) partial remission (PR); one (7%) patient achieved stable disease (SD). Of interest, among rare subtypes, one patient with ALK negative ALCL achieved CR, one with ALK positive ALCL achieved PR, one patient with HSTL achieved PR, and one patient with NK/TCL achieved CR. Median reduction in tumor burden was 65% (range, 0-100%) (Figure 1).

Nine (50%) patients proceeded to SCT (5 allogeneic, 4 autologous) after treatment, after a median time of three months (range, 2-4 months); one additional patient proceeded to allogeneic SCT later during the course of disease, at time of relapse. Among the 7 patients for whom peripheral blood stem cell collection was attempted, collection failed in 2 and median number of $CD34^+$ cells was $5x10^6$/Kg (range, 0-20). One patient, who had an adequate collection, progressed before autologous SCT could be performed. Among 4 patients who underwent autologous SCT, median time to platelet recovery was 28 days (range, 10-43) and median time to neutrophil recovery was 11 days (range, 10-13), though in all cases granulocyte-colony stimulating factor (G-CSF) support was provided.

After a median follow up of 13 months (range, 3-45 months), median progression-free survival (PFS) was ten months (95%CI: 1-21 months). At last follow up, 10 patients have had progression or relapse of disease, 4 after SCT (3 after allogeneic SCT, 1 after autologous SCT). Time to SCT and PFS are shown in Figure 2.

At the most recent follow up, 10 patients have died: 6 of disease progression, one of therapy-related acute myeloid leukemia (while disease was progressing), 2 of pneumonia (while in remission), and one of renal insufficiency while in remission. Median overall survival (OS) was 15 months (95%CI: 10-20 months).

At time of study design, romidepsin had already been approved by the US Food and Drug Administration for the treatment of relapsed PTCL, based on the results of two phase II studies investigating its activity as single agent in this setting.[7,8] With the limits of an inter-study comparison, both hematologic (mainly thrombocytopenia) and non-hematologic toxicities (the most common being fatigue, nausea/vomiting and infections) were more frequent with the combination of romidepsin and ICE, as compared to single agent romidepsin,[7,8] but similar to what has been reported for ICE without romidepsin,[4,5,9,10] reducing the concern for synergistic toxicity.

With the same limits, the ORR (93%) and CR rate (80%) observed in our study were higher than what has been reported with romidepsin monotherapy (ORR 25%-38%, CR 15%-18%)[7,8] or ICE without romidepsin (ORR 70%, CR 35%).[9] However, it is important to consider that in older studies, positron emission tomography was not included in the response assessment, and, as a consequence, CR rate may have been underestimated.

Consolidation with SCT was sought in disease CR. In total, 50% of the enrolled patients proceeded to SCT, with 5 patients proceeding to allogeneic SCT, and 4 to autologous SCT. While autologous SCT is typically preferred, given both the benefit and toxicity risks associated with allogeneic SCT as consolidation after front-line setting, except for very rare aggressive subtypes of PTCL,[11,12] its role in relapsed patients achieving remission after salvage therapy is less clear. Consequently, particularly in the absence of disease CR, allogeneic SCT is often considered in the salvage setting.[13,14]

After a median follow up of 13 months, a median PFS of 10 months and a median OS of 15 months have been reached; this compares favorably with both single agent romidepsin (median PFS, 9 months)[8,15] or ICE without romidepsin (median PFS, 6 months).[5] Interestingly, the majority of progressions occurred among patients who were unable to undergo SCT, and about 30% of observed deaths were not due to disease progression, further highlighting the need for less toxic salvage regimens. Furthermore, many progressed after SCT, raising the question of potential post-transplant maintenance therapy in these patients.

Since 2009, the FDA has approved 4 novel agents for the treatment of patients with relapsed or refractory PTCL, including romidepsin, pralatrexate, belinostat and brentuximab vedotin. In our study we demonstrate that the incorporation of one of these agents, romidepsin, to ICE back-bone salvage chemotherapy can translate into higher CR rate without significant increase in toxicity, facilitating subsequent consolidation with SCT. Our trial

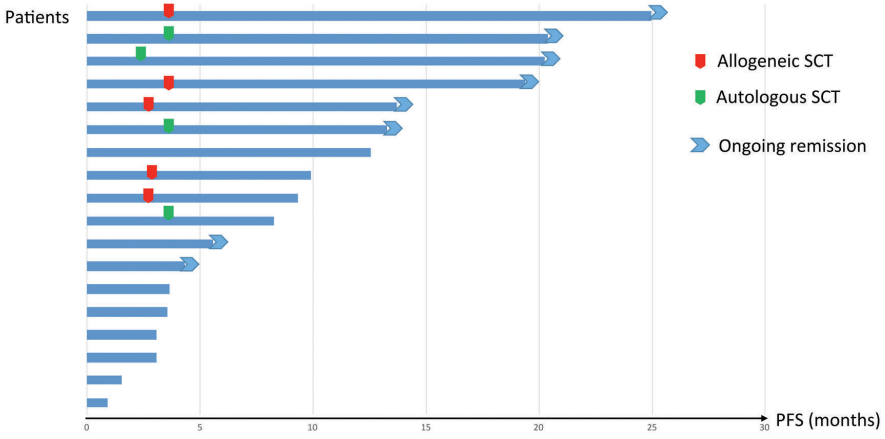

Figure 2. Swimmer plot showing time to stem cell transplant and progression-free survival. SCT: stem cell transplantation; PFS: progression-free survival.

represents an early step towards the integration of targeted therapy into combined treatment strategies for relapsed and refractory PTCL. Multiple trials are currently evaluating chemotherapy-free doublets, and early data suggest potential durable efficacy and a role for such strategy as salvage therapy for PTCL (*clinicaltrials.gov identifiers: 02341014, 01897012, 02783625, 01947140, 01998035*). Additionally, trials investigating the role of maintenance both with romidepsin and with other targeted agents post SCT for patients with PTCL are ongoing (*clinicaltrials.gov identifiers: 01908777, 02512497, 01822509*). It is hoped that these trials will help to reverse the dismal prognosis currently associated with relapsed or refractory PTCL.

Paolo Strati,[1] Dai Chihara,[2*] Yasuhiro Oki,[3] Luis E Fayad,[3] Nathan Fowler,[3] Loretta Nastoupil,[3] Jorge E Romaguera,[3] Felipe Samaniego,[3] Naveen Garg,[4] Lei Feng,[5] Emily T. Wesson,[3] Charnelle E. Ruben,[3] Mildred D. Stafford,[3] Yago Nieto,[6] Issa F Khouri,[6] Chitra Hosing,[6] Sandra B. Horowitz,[3] Rammurti T-. Kamble[7] and Michelle A.Fanale[3]*

[1]Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX; [2]Department of Internal Medicine, University of New Mexico, Albuquerque, NM; [3]Department of Lymphoma and Myeloma, MD Anderson Cancer Center, Houston, TX; [4]Department of Diagnostic Radiology, MD Anderson Cancer Center, Houston, TX; [5]Department of Biostatistics, MD Anderson Cancer Center, Houston, TX; [6]Department of Stem Cell Transplantation, MD Anderson Cancer Center, Houston, TX and [7]Department of Hematology-Oncology, Baylor College of Medicine and Houston Methodist Hospital, TX, USA

**PS and DC contributed equally to this manuscript.*

Funding: this work was supported in part by The MD Anderson Cancer Center Support Grant (P30 CA016672).

Correspondence: mfanale@mdanderson.org;
doi:10.3324/haematol.2018.187617

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013;31(16):1970-1976.
2. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol. 2013;31(25):3100-3109.
3. Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol. 2014;7(1):11.
4. Mikesch JH, Kuhlmann M, Demant A, et al. DexaBEAM versus ICE salvage regimen prior to autologous transplantation for relapsed or refractory aggressive peripheral T cell lymphoma: a retrospective evaluation of parallel patient cohorts of one center. Ann Hematol. 2013;92(8):1041-1048.
5. Zelenetz AD, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz CH. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003;14 Suppl 1:i5-10.
6. Dupuis J, Morschhauser F, Ghesquieres H, et al. Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: a non-randomised, phase 1b/2 study. Lancet Haematol. 2015;2(4):e160-165.
7. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood. 2011;117(22):5827-5834.
8. Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. J Hematol Oncol. 2014;7:11.
9. Horwitz S, Moskowitz C, Kewalramani T, et al. Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral T-Cell lymphomas: Minimal benefit when analyzed by intent to treat. Blood. 2005;106(11):2679.
10. Hertzberg MS, Crombie C, Benson W, Taper J, Gottlieb D, Bradstock KF. Outpatient-based ifosfamide, carboplatin and etoposide (ICE) chemotherapy in transplant-eligible patients with non-Hodgkin's lymphoma and Hodgkin's disease. Ann Oncol. 2003;14 Suppl 1:i11-16.
11. Corradini P, Vitolo U, Rambaldi A, et al. Intensified chemoimmunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia. 2014;28(9):1885-1891.
12. Loirat M, Chevallier P, Leux C, et al. Upfront allogeneic stem-cell transplantation for patients with nonlocalized untreated peripheral T-cell lymphoma: an intention-to-treat analysis from a single center. Ann Oncol. 2015;26(2):386-392.
13. Jantunen E, Wiklund T, Juvonen E, et al. Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transplant. 2004;33(4):405-410.
14. Corradini P, Dodero A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol. 2004;22(11):2172-2176.
15. Pro B, Horwitz SM, Prince HM, et al. Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. Hematol Oncol. 2017;35(4):914-917.