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Phase II trial of romidepsin (FK228 or depsipeptide) in peripheral T-cell lymphoma: clinical activity and molecular markers

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Histone deacetylase inhibitors induce changes in gene expression that lead to cellular differentiation and reversal of the transformed phenotype. In addition, acetylation of centromeric chromatin and non-histone proteins also likely plays a role in cytotoxicity due to romidepsin. Interest in clinical development of these agents has been spurred by the responses observed in patients with peripheral or cutaneous T-cell lymphoma to romidepsin, previously FK228 or depsipeptide. Phase I trials of romidepsin were carried out primarily in patients with solid tumors, where limited activity was seen. Two schedules were tested: a day 1 and 5 schedule at the NCI, administered every 21 days. In this schedule, the maximum tolerated dose was determined to be 17.8 mg/m^2. In a second schedule, days 1, 8 and 15 repeating every 28 days, the maximum tolerated dose was 14 mg/m^2. Responses included one patient with renal cell cancer in the NCI Phase I trial and minimal response or stable disease observed in the Georgetown Phase I trial, in patients with pancreatic cancer and sarcoma. Following completion of the NCI Phase I trial, an additional cohort of patients was enrolled for molecular studies; one patient with peripheral T cell lymphoma had a rapid response to treatment and went on to experience a complete remission of his disease. Based on this observation, and similar responses in patients with cutaneous T cell lymphoma, a Phase II trial was launched.

The index patient was treated for 2 years, when therapy was discontinued after the patient developed prostate cancer. His PTCL continued in complete remission lasting for over 5 years. Recently, the patient was diagnosed with an apparent new peripheral T cell lymphoma, with a distinctive molecular rearrangement.

To date, 61 patients with CTCL and 34 with PTCL have been accrued to our ongoing multiinstitutional trial of romidepsin for patients with recurrent or refractory cutaneous or peripheral T-cell lymphoma. Romidepsin is administered as a 4 hr infusion on days 1, 8, and 15 of a 28 d cycle with a starting dose of 14 mg/m^2. Complete and partial responses have been observed in patients with CTCL, with a complete response in a patient with Sézary syndrome ongoing for over 45 months and a partial response ongoing for over 60 months. Both complete and partial responses were observed in patients with various subtypes of PTCL, including PTCL, unspecified, ALK$^-$/CD30$^+$ anaplastic large cell lymphoma, and enteropathy-associated T-cell lymphoma, with a complete response ongoing for over 34 months. Response data will be updated for presentation.

A preliminary analysis of 26 PTCL patients includes 3 patients with complete remission, and 3 patients with partial remission, for an overall response rate of 24%. Responses were assessed using the International Working Group (*Cheson*) criteria. Patients were also evaluated for the presence or absence of circulating tumor cells by flow cytometry; any evidence of a malignant clone had to resolve prior to considering the disease in complete remission. Among the initial 26 patients, 54% had a performance status (PS) ECOG 1, and 11% a PS ECOG 2. A significant proportion of patients exhibited poor prognostic factors, including 48% of patients with anemia, 19% with a low albumin, and 52% with an elevated LDH. All patients had prior combination chemotherapy, including several who had prior transplant regimens.

As one example, images from one patient with PTCL unspecified are

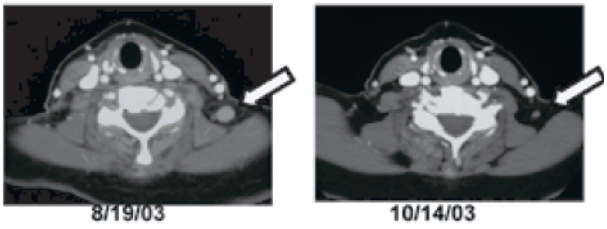

Figure 1. Patient with PTCL responding to romidepsin at 14 mg/m² d 1,8,15.

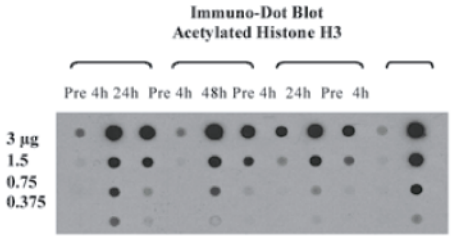

Figure 2. Immuno-Dot Blot Acetylated Histone H3.

shown in Figure 1. This patient was previously treated with CHOP, ESHAP, and VP-16/BCNU/Cytoxan before enrolling on the romidepsin study. The patient experienced a complete remission that was confirmed by PET imaging after 8 months of therapy. She continued on romidepsin for 24 months, when therapy was discontinued. She remains in complete remission one year later.

Principal toxicities observed for romidepsin include fatigue, nausea, vomiting, anorexia, and transient granulocytopenia, lymphopenia, and thrombocytopenia. These toxicities are generally mild, and most patients with responding disease return to work while continuing to receive romidepsin. However, the nausea and vomiting do require prophylaxis with the antiemetic granisetron. Pharmacokinetic parameters in these patients reveal a C_{max} of 501 ng/mL, and a clearance of 15.1/hr (3.8-70.3 l/hr).

Careful cardiac monitoring has been a feature of romidepsin trials since their inception. This was first based on animal studies in which myocardial necrosis was observed at lethal doses of the drug in dose-finding studies, and later based on the observation of ECG changes occurring in patients treated with the agent. These changes are typically characterized by ST-T wave flattening and inversion, lengthening of the QT interval, and a slight increase in heart rate. Extensive cardiac evaluations have shown that these ECG findings are not associated with evidence of myocardial injury. Troponin and CPK blood levels, MUGA scans, and echocardiograms have convincingly demonstrated the absence of myocardial toxicity. The one question that remains is whether romidepsin could potentiate cardiac arrhythmias in patients with underlying cardiac disorders. Sudden death occurred in five patients enrolled on various clinical trials with romidepsin. Each of the patients had one or more risk factors for sudden death; several with major risk factors. Since this observation, no patients with risk factors for sudden cardiac death are enrolled on clinical trials of romidepsin. The ECG findings appear to be a class effect of the histone deacetylase inhibitors, so it will be important to investigate and identify any electrophysiologic effects of all of the agents. A preliminary analysis of routine telemetry monitoring of patients treated at the NIH Clinical Center did not identify an obvious increase in ectopic activity after treatment with romidepsin.

Molecular endpoint analysis was performed in normal and malignant circulating peripheral mononuclear cells, PBMCs, and in tumor samples. Among 45 patients with T cell lymphomas enrolled on the Phase II trial, immunoblot analysis demonstrated increased histone acetylation in PBMCs of 2-fold or greater from 19 of 33 patients at 4 or 24 hrs. Early studies with the NCI Drug Screen recognized romidepsin as a substrate for Pgp-mediated drug resistance, and, through its activity as a histone deacetylase inhibitor, an agent able to induce MDR-1. Thus, MDR-1 analysis has been carried out as a surrogate for the effects of HDAC inhibition and as a probe for the onset of drug resistance. RT-PCR of RNA demonstrated a 2-fold or greater increased expression of MDR-1 in PBMCs from 27 of 45 patients, 11 of which were greater than 4-fold. MDR1 expression was evaluated by RT-PCR in 30 patients' tumors. Strikingly, MDR1 expression level was not significantly increased at the time of disease progression, mean 3.2 and 4.9 (s.d. 3.1 and 5.5, respectively) in MDR1 units as defined in Zhan *et al.* Blood 1997 89:3795. Since differentiating agents have been shown to induce expression of fetal hemoglobin in the laboratory, fetal hemoglobin levels were assayed in patients on this clinical trial. Increased circulating fetal hemoglobin of 2, 5, and 10 fold was observed in 34, 24, and 15 patients, respectively, from 44 patients evaluated.

In conclusion, romidepsin has significant single agent activity in patients with CTCL and

PTCL. Molecular effects can be assayed in patients treated with romidepsin and related agents. Further clinical development of these agents should include combination trials and the identification of molecular markers of response. The differentiation effect of romidepsin may also be useful for the treatment of other conditions, such as the hemoglobinopathies.

Based on responses observed in CTCL, a registration study with romidepsin has been initiated by Gloucester Pharmaceuticals and is ongoing and Fast Track designation from the FDA has been obtained. The results reported in this abstract suggest that a histone deacetylase inhibitor such as romidepsin should also be pursued in peripheral T cell lymphoma. The long duration of remission in patients who have previously experienced repeated treatment failure is exceptional and deserving of intensive study. Based on these data, a registration study in PTCL is planned to initiate in 2006.

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