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Low-Dose Electron Beam Radiation and Romidepsin Therapy for Symptomatic Cutaneous T-Cell Lymphoma Lesions

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Abstract

BACKGROUND—Romidepsin is a structurally unique histone deacetylase inhibitor FDA-approved for therapy of relapsed or refractory cutaneous T-cell lymphoma (CTCL). Localized electron beam radiation therapy (LEBT) is standard practice in the care of patients with chronically traumatized and painful lesions. Combinational therapy of those two modalities may be beneficial for the therapy of CTCL.

OBJECTIVES—To report observations on supportive LEBT utilized for isolated refractory lesions in patients on romidepsin.

METHODS—Observations during a phase 2 clinical trial sponsored by the National Cancer Institute (NCI 1312) examining the efficacy of romidepsin for patients with relapsed, refractory, or advanced CTCL, stage IB-IVA mycosis fungoides (MF) or Sézary syndrome. Skin responses were assessed by evaluation of five target lesions only. Patients with objective clinical responses in target lesions who had symptomatic non-target lesions were allowed limited localized radiation to isolated lesions for symptomatic relief. Patients who received localized radiation were not considered complete responders at any point.

RESULTS—Five patients with advanced MF (3 had stage IIB and 2 had stage IVA2) received localized electron beam radiation to symptomatic non-target lesions while on a protocol with romidepsin. None of these patients experienced additional or unexpected toxicity. Four of the five patients demonstrated fast and durable responses. We noted that significantly lower than standard doses of electron beam radiation effectively treated symptomatic lesions in these patients.

CONCLUSIONS—Electron beam therapy demonstrated significant responses at very low doses without additional toxicity in patients on protocol treatment with the histone deacetylase inhibitor romidepsin. This merits formal investigation in a clinical trial for potential synergy in patients with cutaneous T-cell lymphoma.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of epidermotropic non-Hodgkin lymphomas.[1] Several Food and Drug Administration (FDA)-approved single

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agents are available for the treatment of CTCL; reported response rates range from 25% to 60%,[2] highlighting the need to improve response rates and sustain remissions.

Localized electron beam radiation (LEBT) is an effective therapy for cutaneous lesions of CTCL because of the radiosensitivity of malignant lymphocytes and is used routinely as a part of the treatment algorithm for therapy at all stages of CTCL.[2,3]

Histone deacetylase (HDAC) inhibitors are a class of chemotherapeutics that target the deacetylase family of enzymes. Romidepsin (FK228, FR901226, depsipeptide), like other HDAC inhibitors, has been shown to induce cell cycle arrest in both G and $G_{1\ 2}$/M phases and to induce apoptosis. [4] Monotherapy of CTCL with romidepsin has been characterized by vigorous clinical responses. Two recently completed phase 2 multi-centre clinical trials[5,6] that examined the efficacy of romidepsin as monotherapy for patients CTCL supported FDA approval of the drug for clinical practice.

Herein, we present responses and safety profile of low dose electron beam radiation administered to symptomatic non-target lesions during romidepsin therapy in patients with objective clinical responses.

MATERIALS AND METHODS

In NCI 1312, 'Phase II Trial of Depsipeptide in Patients with Cutaneous T-Cell Lymphoma and Relapsed Peripheral T-Cell Lymphoma' (ClinicalTrials.gov identifier NCT00020436), romidepsin was administered as a 4-hour infusion at 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. The dose of infusion was lowered by 25%, if the patient had absolute granulocyte count ≥500/μl, but <1000μl, or platelet count ≥50,000/μl, but <75, 000/μl. The assessment of CTCL resolution were performed in all compartments including skin, lymph nodes, viscera, and blood and were efficacy endpoints in NCI1312. Disease in the skin or viscera was assessed by Response Evaluation Criteria In Solid Tumours (RECIST) criteria;[7] up to five target skin lesions were selected and monitored for response. Lymph node disease and bone marrow involvement was assessed using International Working Group guidelines,[8] and blood was assessed by flow cytometry. Patients with ongoing clinical response according to the RECIST criteria were allowed to have radiation to symptomatic non-target lesions. These patients received LEBT to isolated lesions as per protocol, allowing them to continue systemic therapy. Radiation therapy was not administered on days patients received romidepsin. No other topical or concurrent systemic therapy was allowed per protocol. Patients who received radiation while on protocol were not categorized as having a complete response at any time.

RESULTS

Five patients, including 3 from the first report of 71 patients enrolled on NCI 1312 and 2 who enrolled subsequently, received LEBT as supportive care to non-target lesions that were painful or otherwise symptomatic compromising their quality of life, while significant and durable clinical responses were otherwise demonstrated. Four of the five patients achieved a partial response (PR) to romidepsin therapy with an average reduction of 41% (range from 34% to 72%) in target lesion size by RECIST prior to radiation therapy. Despite evidence of clinical benefit, there were non-target lesions that were chronically traumatized, inflamed, and caused severe pain. Because the overall response rate on the skin was based primarily on target lesions, low dose LEBT to such lesions did not interfere with response assessment. LEBT to symptomatic lesions was administered according to Fig. 1 and Table 1 with significant improvement or complete resolution of the irradiated lesions (Fig. 2). Patient 1 remains on intermittent treatment with romidepsin now 10 years after study enrolment.

Patient 3 was removed from study after 24 months of therapy with romidepsin and while off study, the patient resumed treatment with romidepsin and has remained in clinical remission for 2 years. Three patients developed disease progression outside the irradiated areas and romidepsin was discontinued. No adverse reactions were observed following irradiation, and there was no evidence of a radiation recall phenomenon in subsequent cycles.

DISCUSSION

We described the clinical experience in five patients who received low dose LEBT to symptomatic non-target lesions during the romidepsin clinical trial NCI1312. Four of five patients experienced rapid and durable clinical responses at the radiotherapy site, suggesting that *in vitro* reports of synergy between romidepsin and LEBT may be clinically relevant.[9] Use of LEBT was only a supportive care measure and was not formally built in or optimized as part of the clinical trial. Importantly, there was no additional or unexpected toxicity observed at the sites of irradiation at the doses provided.

Recently, Kamstrup et. al. explored the possibility of using lower radiation doses for total skin electron beam therapy, which could limit toxicity and allow this treatment to be repeated for long-term disease control.[10] Low-dose total skin electron beam as monotherapy produced only short-lived responses in this cohort. However, there are significant preclinical data suggesting that HDAC inhibitors, especially romidepsin, may show synergy when used with electron beam or other therapeutic modalities such as ultraviolet irradiation. Radiosensitization seems to be a class effect of HDAC inhibitors,[11] and the radiosensitizing activity of romidepsin has been demonstrated in vitro in human squamous carcinoma, gastric adenocarcinoma, and colon carcinoma cell lines.[9,12]

Several mechanisms have been proposed to explain this sensitization. Because the sites of active transcription are generally more sensitive to radiation, relaxation of chromatin due to HDAC inhibition may lead to increased sensitivity.[13] Alternatively, cumulative cell cycle effects may play a role; romidepsin at therapeutic concentrations arrested lymphoma cell lines primarily in G_1,[14] whereas ionizing radiation led to G_2/M arrest.[15] Downregulation or increased acetylation of DNA repair proteins has been proposed as a mechanism of reduced radiation-induced DNA double-stand break repair, and the observation of prolonged phosphorylated histone H2AX is consistent with that hypothesis.

We have shown that LEBT can be safely used with romidepsin and was effective across all doses including very low doses of radiation. Due to the fact that our observations were not done in systematic or controlled manner, we cannot conclude whether there is a synergy of radiation and HDAC inhibitor therapy based on our data. However, taken together with demonstrated synergy *in vitro,* our clinical observations of durable clinical responses in the patients receiving very low doses of radiation are suggestive of such synergy. Therefore, prospective randomized clinical trial to evaluate low doses of EBT during HDAC therapy to formally evaluate their synergy and to establishing the therapeutic schedule and to assess their efficacy is warranted.

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SUMMARY

What's already known about this topic? In vitro studies reported synergy between romidepsin and electron beam therapy due to radiosensitization of malignant lymphocytes by HDAC inhibitors.

What does this study add? Our observations show that standard of care low-dose localized electron beam therapy for treatment of cutaneous T cell lymphoma can be administered safely and effectively while a patient is receiving romidepsin. There was no additional or unexpected toxicity observed.

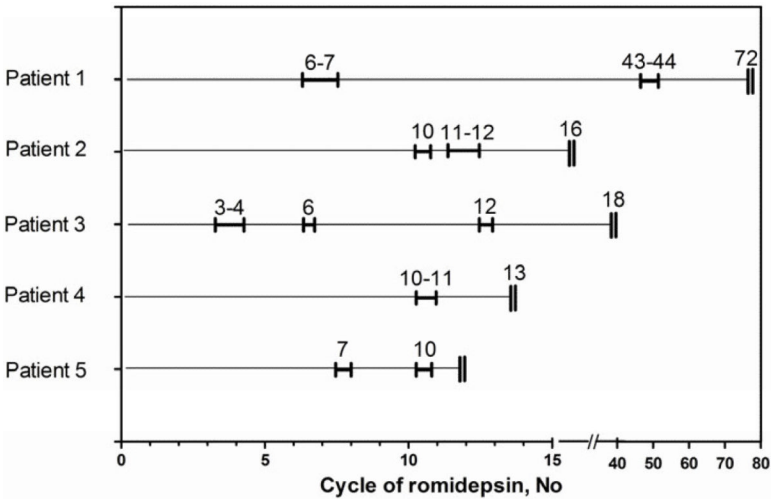

Figure 1.

Time of administration of LEBT during the course of romidepsin. Five patients with symptomatic lesions received LEBT. Thin lines across for each patient represent a course of therapy with time of LEBT administration bracketed. A double vertical line at the end shows when disease progression was declared, or for patient 1, therapy with romidepsin stopped.

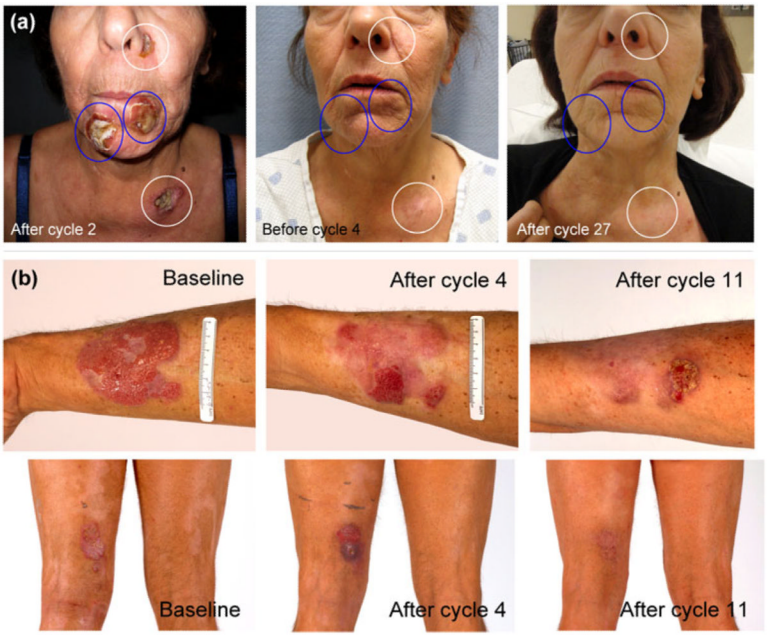

Figure 2.

(a) Patient 3. Tumors treated with romidepsin (white circles) or romidepsin and localized electron beam therapy (LEBT) (blue circles). Sustained clinical remission with complete resolution of tumors. **(b)** Patient 5. Lesions at baseline and after 4 or 11 cycles of romidepsin. Upper panels: forearm plaque with response to romidepsin alone. Lower panels: posterior thigh plaque, which became ulcerated but cleared with irradiation with 10 Gy in 5 fractions during cycle 7.

Table 1

Percentages of the body surface area of irradiated region in comparison with initial involvement of cutaneous T-cell lymphoma at enrollment and regimen of irradiation

Patient	Age/Race/Sex	Stage	On-study TBSA	BSA irradiated	Type of lesions	Cycle	Energy	Dose per fraction	No. of fractions
1	41/W/M	IIB	16%	2.5%	plaques	6-7	9 MeV	180 cGy	20
				2.0%	plaques	43-44	6 MeV	180 cGy	20
2	41/W/F	IVA2	91.5%	8.6%	papules	10	6 MeV	600 cGy	4
				9.7%	papules	11	6 MeV	400 cGy	6
				10.7%	plaques	12	6 MeV	400 cGy	8
3	61/W/F	IIB	0.8%[a]	0.3%	tumors	3	6 MeV	400 cGy	12
				0.1	tumors	4	6 MeV	400 cGy	4
				0.1	tumors	6	6 MeV	400 cGy	6
				0.01	tumor	12	6 MeV	400 cGy	2
4	34/AA/F	IVA2	82%	6%	plaques	10 - 11	6 MeV	180 cGy	10
5	42/W/M	IIB	36.5%[b]	2.9%	tumors	7	6 MeV	200 cGy	5
				2.0%	plaques	10	6 MeV	200 cGy	5

TBSA, Total Body Surface Area for patches and plaques only; BSA, Body Surface Area;

[a] All CTCL lesions were tumors.

[b] Patient had tumors occupying additional 10% of TBSA