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Romidepsin for the treatment of relapsed/refractory cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome): Use in a community setting

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ABSTRACT

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of rare non-Hodgkin lymphomas that arise in the skin. In advanced stages, CTCL becomes systemic and is associated with poor prognosis. Diagnosis of CTCL and treatment of early-stage disease with topical therapies often occurs under the care of a dermatologist. Community oncologists see few patients with CTCL due to direct referrals from dermatologists to academic or lymphoma specialty centers. However, some patients will continue to be managed in a community setting. Currently there is no evidence-based stepwise algorithm for treatment of patients with CTCL, and guidelines suggest a wide range of systemic therapies, including biologics, targeted agents, and more traditional chemotherapies. To provide optimal care in a community setting, oncologists must become familiar with newer nonchemotherapeutic treatment options. This review highlights romidepsin, a histone deacetylase inhibitor approved for the treatment of patients with CTCL who have received ≥1 prior systemic therapy.

1. CTCL overview and epidemiology

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of non-Hodgkin lymphomas (NHL) in which malignant, mature, post-

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thymic T cells initially arise in the skin (Lansigan et al., 2008). The most common type of CTCL is mycosis fungoides (MF) (Criscione and Weinstock, 2007; NCCN, 2016), and CTCL is sometimes referred to by the common subtypes MF and Sézary syndrome (SS, leukemic variant) (NCCN, 2016). Rare non-MF/SS CTCL subtypes and their treatment vary widely, and it is beyond the scope of this review to discuss them in detail. NHL accounts for ≈4% of all cancers diagnosed in the United States (US), with 72,580 estimated new cases in 2015 (American Cancer Society, 2016) and a US prevalence of 569,536 people in 2013 (National Cancer Institute, 2016). CTCL accounts for ≈4% of NHL cases in the US (Criscione and Weinstock, 2007; Leukemia and Lymphoma Society, 2016), with ≈3000 new cases diagnosed per year (American Cancer Society, 2016). CTCL typically affects older people, with a median age at diagnosis reported at 54 years old (Agar et al., 2010), and rates increase exponentially with age (Korgavkar et al., 2013; Imam et al., 2013). However, CTCL does occur in younger people, including children (Crowley et al., 1998; Pope et al., 2010). Additionally, there is a ≈1.5:1 male:female and black:white predominance in CTCL cases (Korgavkar et al., 2013; Imam et al., 2013).

In early stages, CTCL is confined to the skin but can progress to systemic disease (lymph node, blood, visceral organs), resulting in significantly reduced survival (Olsen et al., 2007a; Klemke et al., 2005). Other than patients with stage IA disease, patients with CTCL have worse overall survival (OS) than that of age-, sex-, and race-matched control populations (Talpur et al., 2012). Median OS for patients with later-stage disease (≥IIB) is <5 years (Agar et al., 2010). However, the time frame for disease progression can differ extensively; some patients will remain in early stages for decades, while others progress to later-stage disease (Leukemia and Lymphoma Society, 2016).

2. Presentation and diagnosis

Patients with undiagnosed CTCL typically present to a dermatologist with the appearances of patches or plaques of unclear etiology. The time from initial symptoms to diagnosis is often several years (Mishra and Porcu, 2011) because early-stage CTCL frequently resembles more benign conditions, such as eczema or psoriasis, and may initially show improvement with topical corticosteroids or other common therapies for these conditions (Parker and Bradley, 2006; Zackheim and McCalmont, 2002). Early symptoms of CTCL are typically dry skin and/or a rash (red, dark, or light skin patches), often with itching (pruritus) (Leukemia and Lymphoma Society, 2016). However, visible skin changes as a result of CTCL vary widely and may include scaly red rash or discolored patches in areas not usually exposed to sun; thin, reddened, eczema-like rash; thickened scaly, red skin (or plaques) or psoriasis-like rash; and/or erythroderma (skin redness, often with scaling) (Leukemia and Lymphoma Society, 2016). Upon early presentation, pathology, appearance of skin lesions and clinical presentation may not support the diagnosis. In time, the clinicopathologic picture will lead to a diagnosis of CTCL. Both erythroderma and the appearance of tumors should increase the index of suspicion of an alternative diagnosis. The visibility of skin changes as a result of CTCL can affect patients both physically and emotionally, impacting their quality of life (QoL) (Leukemia and Lymphoma Society, 2016; Parker and Bradley, 2006). Additionally, even in early-stage disease, patient QoL can be significantly impacted by pruritus—often described as debilitating as a result of discomfort and inability to sleep or perform daily activities (Parker and Bradley, 2006; Meyer et al., 2010; Demierre, 2010; Ahern et al., 2012; Vij and Duvic, 2012; Demierre et al., 2006).

Patients also frequently experience skin infections as a result of breakdown of the skin at lesion sites (Leukemia and Lymphoma Society, 2016; Parker and Bradley, 2006). Unmanageable infections can result in sepsis and death in patients with CTCL (Axelrod et al., 1992; Tsambiras et al., 2001). Maintaining a low index of suspicion for potential skin infections and secondary sepsis is important. Obtaining skin culture of wounds and other areas as indicated is of vital importance and provides guidance for therapy, particularly for patients treated with frequent antibiotics. Oncologists should also have a low index of suspicion for viral infection and appropriate skin cultures should be taken. Although viral infection is less common, proper management to prevent it is essential. Skin care, especially for those with skin breakdown, can be very complicated, and collaborating with dermatologists and a multidisciplinary center will aid in dealing with these varied presentations (Poligone and Querfeld, 2015). The importance of aggressive management of secondary skin issues cannot be understated because it will generally reduce death and morbidity from sepsis/skin infection. Furthermore, appropriate management of skin infections can clarify during the skin exam what is and is not disease.

Diagnosis of CTCL is often confirmed under the direction of a dermatologist, and requires a series of tests and procedures, including physical examination and history of treatments to the skin lesions, skin biopsies along with clinicopathologic correlation (histopathology, immunohistochemistry, molecular analysis), lymph node biopsies—particularly in the absence of definitive skin diagnosis, and assessment of peripheral blood for the presence of malignant T-cells (Sézary cells) (Jawed et al., 2014a). A narrative review of the diagnosis of CTCL was recently published (Jawed et al., 2014a).

3. Staging and prognosis

Staging of CTCL is based on disease involvement in the skin, lymph nodes, blood, or visceral organs (Table 1) (Olsen et al., 2007a). Workup to determine staging should include at a minimum a complete physical examination, including skin exam, assessment of the percentage of body surface area involvement and type(s) of lesions (Olsen et al., 2011), and palpation of peripheral lymph node regions and other masses. Appropriate laboratory studies include complete blood count, assessment of Sézary cells (and

Table 1
ISCL/EORTC Staging System for CTCL and Disease Presentation and Survival by Stage.

Stage	Classifications (Olsen et al., 2007a)				Presentation by Stage, n (%) (Agar et al., 2010)	Median Survival by Stage, years (Agar et al., 2010)
IA	T1	N0	M0	B0-1	438 (29)	35.5
IB	T2	N0	M0	B0-1	583 (39)	21.5
IIA	T1-2	N1-2	M0	B0-1	40 (3)	15.8
IIB	T3	N0-2	M0	B0-1	167 (11)	4.7
IIIA	T4	N0-2	M0	B0	100 (7)	4.7
IIIB	T4	N0-2	M0	B1	56 (4)	3.4
IVA_1	T1-4	N0-2	M0	B2	67 (5)	3.8
IVA_2	T1-4	N3	M0	B0-2	37 (3)	2.1
IVB	T1-4	N0-3	M1	B0-2	14 (1)	1.4

CTCL, cutaneous T-cell lymphoma; EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; NCI, National Cancer Institute.
T (skin): T1, limited patch/papule/plaque (<10% body surface area [BSA]); T2, generalized patch/papule/plaque (≥10% BSA); T3, tumors; T4, generalized erythroderma (≥80% BSA).
N (nodes): N0, no clinically abnormal peripheral lymph nodes; N1, N2, N3, clinically abnormal peripheral lymph nodes with histopathology Dutch grade 1/NCI LN0-2, Dutch grade 2/NCI LN3, Dutch grade 3–4/NCI LN4, respectively (clone +/−).
M (viscera): M0, no involvement; M1, visceral involvement.
B (blood): B0, absence of significant blood involvement (Sézary cells <5% of peripheral blood lymphocytes, clone +/−); B1, low tumor burden (Sézary cells >5% of peripheral blood lymphocytes without meeting criteria for B2, clone +/−); B2, high blood tumor burden (Sézary cells ≥1000/μL of peripheral blood lymphocytes with clone +).