Cutaneous T-Cell Lymphoma in Sub-Saharan Africa

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Abstract
The incidence and economic burden of cancer in sub-Saharan Africa is increasing, and innovative strategies are needed to improve prevention and care in this population. This article uses a case of cutaneous T-cell lymphoma in Uganda to propose guidelines for the diagnosis and treatment of this disease in resource-limited settings. These guidelines were developed from the consensus opinion of specialists at the Uganda Cancer Institute and Fred Hutchinson Cancer Research Center as part of an established collaboration. Areas for future investigation that can improve the care of patients in this region are identified. (JNCCN 2013;11:275–280)

Cutaneous T-cell lymphomas (CTCL) constitute 2% of all non-Hodgkin’s lymphoma diagnoses in the United States. The most common subtypes are mycosis fungoides (MF) and its leukemic presentation, Sézary syndrome (SS). CTCLs were noted to occur with a higher incidence rate among African-Americans in a recent analysis of SEER data, and although no studies estimate the prevalence of CTCL or MF in sub-Saharan Africa (SSA), many case series have suggested that the diagnosis is more frequent than currently recognized. Data are insufficient to clearly recommend one treatment regimen over another, and although several treatment guidelines for CTCL exist in resource-abundant regions, this is not true for resource-limited settings.

In 2008, a formal collaboration between the Uganda Cancer Institute (UCI) and the Fred Hutchinson Cancer Research Center (FHCRC) was initiated with a tripartite mission: 1) to conduct research to reduce the incidence, morbidity, and mortality associated with cancers seen commonly in the United States and SSA; 2) to build the capacity for global cancer research and care; and 3) to develop novel strategies for the treatment and prevention of infection-related cancers and cancers of high incidence in resource-limited settings. As part of this ongoing collaboration, 2 clinical cases are selected each month from the more than 800 seen monthly at the UCI that represent opportunities for improving cancer care. Multidisciplinary experts from both institutions discuss cases via Web-conference between the Seattle and Kampala clinical sites, and come to consensus regarding knowledge gaps and opportunities to develop standards of care in resource-limited settings. This article describes a recent case of CTCL in Uganda from the conference, and summarizes the subsequent discussion to outline an approach to care that may be appropriate for other resource-limited settings in SSA.

Case Presentation
A 75-year-old man from Kampala, Uganda, presented to Mulago Hospital reporting a 7-year history of gradually increasing pruritus and diffuse, scaly skin lesions (Figure 1A). More recently he reported mild weight loss and anorexia, although he denied having drenching night-sweats or fevers. He denied any palpable adenopathy, but described the
development of a nodular lesion on his face over the past year (Figure 1B). On presentation to the Dermatology Department at Mulago Hospital, he was given a presumptive diagnosis of dermatitis thought to be secondary to exposures in his capacity as a building inspector, and was started on empiric antihistamines and topical corticosteroid therapy. Because of an inadequate response to these agents, he returned for further evaluation, which included a skin biopsy of a lesion on his left shoulder in March 2012.

Histopathologic evaluation suggested an atypical dermal lymphoid infiltrate, although a more specific diagnosis was not possible with the available samples. Therefore, he underwent a repeat skin biopsy of a patch lesion on his anterior chest, which revealed a diffuse dermal infiltrate of lymphoid cells, some with cerebriform nuclei within a collagenous background. No evidence of large cell transformation was noted. To confirm the diagnosis, the local pathologist used his personal supply of antibodies (because routine immunohistochemistry is not available in Uganda), which confirmed that the lymphoid cells stained positive for CD3 and CD45 without CD20 expression.

Based on these results, the patient was diagnosed with CTCL consistent with MF, and was started on 25 mg of oral methotrexate weekly. Because of an inadequate response to methotrexate, he was referred for evaluation at the UCI, where he was determined to have an ECOG performance status of 1 and no additional past medical history was found to be significant. He was noted to be thin but in no acute distress. The skin lesions were immediately evident on evaluation, and were found to be diffuse, scaly patches and plaques involving approximately 30% of his body surface area. Most of the involved areas were on the scalp, trunk, and arms. A tumor-stage lesion measuring 3 cm in maximum dimension was present at the bridge of his nose. No significant adenopathy or splenomegaly was noted. Laboratory evaluation revealed eosinophilia with mild anemia and a normal platelet count. He had renal insufficiency (creatinine level, 2.35 mg/dL [208.6 µmol/L]) and was HIV-negative. Peripheral blood smear examination did not reveal any circulating Sézary cells, although it confirmed the eosinophilia.

Further radiologic evaluation included a chest radiograph without evidence of an enlarged mediastinum, and abdominal ultrasound did not reveal any adenopathy or splenomegaly. Therefore, he was diagnosed with stage IIB (T3,N0,M0,B0) MF on completion of this evaluation.

Discussion

Diagnosis

Diagnosis of CTCLs is difficult even in resource-abundant regions of the world. A long follow-up and evaluation of multiple biopsies are often necessary to confirm the diagnosis. If a tumor-stage lesion is present, a biopsy is typically performed to evaluate for large-cell transformation. Otherwise, the most
indurated lesion is usually selected. Before a biopsy is performed on an involved early-stage skin lesion, therapy is typically held for 2 to 4 weeks because the treatment effect can obscure the characteristic histologic features, including epidermotropism and the cerebriform nuclear appearance. To facilitate the diagnosis in resource-rich settings, clinicopathologic criteria were proposed by Pimpinelli et al.7 Although these criteria can support a diagnosis of MF with clinical and histopathologic findings alone, most cases require adjunctive polymerase chain reaction and/or immunohistochemistry testing, including staining for CD2, CD3, CD4, CD5, CD7, and CD8.7

Because cost constraints preclude assessment of multiple immunophenotypic markers in SSA, a consensus was reached that, in resource-limited settings, the combination of characteristic clinical findings, morphologic appearance on hematoxylin-eosin staining, and a positive CD3 or CD4 immunohistochemical result is sufficient to diagnose MF (Table 1). Clearly, new approaches are needed to develop cost-effective methods to increase the diagnostic capacity in SSA.

In addition to overcoming these challenges associated with diagnosing CTCL, an additional potential neoplasm, adult T-cell leukemia/lymphoma (ATLL), should be considered when diagnosing MF in Africa. Human T-cell lymphotropic virus 1 (HTLV-1) is endemic in parts of Africa, Japan, and the Caribbean (Figure 2) and was first identified in cells from a patient diagnosed with CTCL.8 Since this discovery, a smoldering clinical subtype of ATLL was described that can mimic CTCL clinically and pathologically.9–11 According to the Shimoyama classification, these patients may have progressive skin lesions that develop over many years, a normal serum calcium concentration and lactate dehydrogenase level, no visceral organ involvement, and a skin biopsy with small T lymphocytes and even Pautrier microabscesses, just as in CTCL. A diagnosis of smoldering ATLL requires either the presence of greater than 5% abnormal circulating T lymphocytes in the peripheral blood or the histologic confirmation of typical “flower cells” in a T-cell infiltrate (not present in this case).12 Although the rare patient carries HTLV-1 but has a negative serum antibody test to the virus, this serologic test for HTLV-1 can help differentiate smoldering ATLL of the skin from CTCL. Immunohistochemistry for CD25 may also be helpful, because it is expressed strongly in almost all cases of ATLL. Because HTLV-1 is not endemic in Uganda, these tests were not necessary in the described case.

### Treatment

Patients with CTCL are typically divided into early-stage (IA, IB, IIA) and advanced-stage (IIB, III, IV), because the first group should be treated with skin-directed therapy, whereas the latter is treated predominately with systemic therapy (Table 2).

**Early-Stage Disease:** Early-stage (IA, IB, IIA) CTCL (65%–85% of all patients) is not associated with a change in overall survival when compared with an age-matched population, and early therapy has not been shown to impact the rate of progression. Therefore, the goal of treatment in this setting...

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### Table 1 Clinicopathologic Criteria for the Diagnosis of Mycosis Fungoides in Resource-Limited Settings

<table>
<thead>
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<th>Diagnostic Guidelines</th>
<th>Clinical</th>
<th>Histopathologic</th>
<th>Immunohistochemistry</th>
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<tr>
<td>Required</td>
<td>Persistent and/or progressive patches/thin plaques</td>
<td>Superficial lymphoid infiltrate</td>
<td>Infiltrating cells are CD3+ or CD4+</td>
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<tr>
<td>Supportive</td>
<td>Non-sun-exposed skin</td>
<td>Epidermotropism without spongiosis</td>
<td>CD2+, CD3+, CD5+</td>
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<tr>
<td></td>
<td>Size/shape variation</td>
<td>Lymphoid atypia (enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours)</td>
<td>CD7-, CD8-, CD25-</td>
</tr>
<tr>
<td></td>
<td>Poikiloderma</td>
<td>Circulating Sézary cells Absence of flower cells</td>
<td>Epidermal/dermal discordance of CD2, CD3, and CD5 (aberrant loss in epidermis)7</td>
</tr>
<tr>
<td>Large-cell transformation</td>
<td>Systemic symptoms Tumor-stage lesions</td>
<td>&gt;25% large lymphoid cells within dermal infiltrates</td>
<td>CD3+ May be CD30+/-</td>
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</table>
is to improve symptoms with minimal associated toxicity. In the absence of significant symptoms, patients with early-stage CTCL can be expectantly managed without additional therapy.

The main therapeutic options for early-stage CTCL in resource-limited settings include topical corticosteroids, radiation therapy, and heliotherapy; heliotherapy generally takes the place of controlled phototherapy, which is usually not available. Topical corticosteroids lead to a complete response (CR) in approximately 60% of patients with T1 disease, with an additional 30% experiencing a partial response (PR). Patients with T2 disease also fare well, with 25% CR and 50% PR rates, respectively.14

In the setting of diffuse lesions or inadequate response to corticosteroids, heliotherapy should be considered. The optimal dose of heliotherapy, although never specifically studied in CTCL, can be estimated with data from a South African study that measured the natural ultraviolet B (UVB) exposure at meteorologic centers in Cape Town, Durban, and Pretoria throughout an entire year. In patients with Fitzpatrick skin type VI, 0.08 J/cm² is the initial recommended daily treatment dose (0.03 J/cm² in type III skin) for CTCL. Previous studies show that 70% of the minimal erythema dose is effective in treating MF, with the daily dose increased by 15% every 3 days until the maximum tolerated dose (MTD) is reached.15 This MTD is then maintained throughout the treatment course. To reach these UVB targets with heliotherapy, a patient in Pretoria at 10 AM with type VI skin, for example, requires 77 minutes of sun exposure to all affected areas in December, 113 minutes in March, and 228 minutes in June (one-third of this time is required for type III skin in each instance). Because an equatorial country such as Uganda has less seasonal variation and more intense UVB exposure, these durations are likely overestimates for that region, although a significant amount of time is still required to achieve therapeutic UVB doses using natural sunlight, especially in dark-skinned individuals.

Although the availability of radiation therapy is limited in SSA, some centers such as the UCI do have access to this modality, usually with a cobalt-60 source. Prior studies support the efficacy of cobalt-60 radiation for the treatment of CTCL, with the most durable responses reported for lesions treated with at least 3000 cGy at 200 cGy per fraction.17 Because more recent reports suggest that acceptable disease control (94% CR) is possible with lower doses (400–900 cGy) of radiation delivered in a single fraction,18 consideration should be given to this approach in SSA to optimize the use of radiation therapy and associated costs.

Second-line options for patients with early-stage CTCL in resource-limited settings include topical chemotherapeutics, such as mechlorethamine or carmustine, and low-dose oral methotrexate (MTX). Although no prospective studies have investigated weekly oral MTX, Zackheim et al19 described 69 previously treated patients (60 with T2 disease) who received weekly oral MTX, and reported a CR rate of 12% and a 22% PR rate in patients with T2 disease, with a median time to treatment failure of 15 months. Notably, almost half of these patients received another concurrent therapy at the same time as MTX. The median weekly dose was 25 mg with a maximum dose of 75 mg. In patients who did not experience an initial response, the dose was increased until response occurred or dose-limiting toxicity was noted. Seven patients with tumor-stage disease were described in this retrospective analysis, with only 1 PR described, suggesting that this strategy is of limited value in advanced-stage disease.
Advanced-Stage Disease: In contrast to patients with early-stage disease, advanced-stage disease impacts overall survival. Optimal skin care is crucial in these patients because a common cause of death in patients with CTCL is infection originating from the skin. Because therapy is not expected to be curative, optimal control of symptoms while minimizing the risk of infection is the goal of treatment. Because of cost constraints, many agents are not yet available in resource-limited settings (eg, vorinostat, bexarotene, romidepsin, pralatrexate), and therefore this discussion of advanced-stage disease focuses on the use of traditional cytotoxic chemotherapy, such as gemcitabine and doxorubicin.

Duvic et al\(^\text{20}\) reported an overall response rate of 68% (8% CR; n=25) to gemcitabine at a dose of 1000 mg/m\(^2\) given on days 1, 8, and 15 every 28 days in patients treated previously with a median of 5 prior regimens. In the front-line setting, Marchi et al\(^\text{21}\) reported a 75% overall response rate (22% CR; n=32) at a dose of 1200 mg/m\(^2\) given on days 1, 8, and 15 every 28 days for 6 cycles. Toxicities included mild cytopenias, but it was otherwise well tolerated. The median duration of response in those that experienced a CR was 10 months.

Most of the literature on anthracycline monotherapy in CTCL reports on the use of liposomal doxorubicin, with an overall response rate of 56% (20% CR) reported in a prospective study of advanced-stage CTCL.\(^\text{22}\) Notably, no reports have been published on the response rate to doxorubicin monotherapy in CTCL, because prior studies used this agent in combination regimens.\(^\text{23}\) Evaluating the activity of doxorubicin monotherapy could contribute to more cost-effective treatment of CTCL and help lessen the impact of any future shortages of the liposomal variant.

In the setting of refractory or transformed disease with an aggressive growth rate, combination chemotherapy can be considered, as detailed in Table 2. However, extrapolation of the experience with aggressive regimens developed in resource-abundant settings can lead to significant toxicity in SSA. For example, treatment of endemic Burkitt lymphoma in Malawi with a dose-reduced version of the LMB 89 Group B protocol led to a 33% treatment-related mortality compared with less than 1% reported in the original European cohort.\(^\text{24,25}\) Therefore, combination regimens should be delivered with caution, and only in centers able to provide adequate supportive care.

<table>
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<th>Table 2</th>
<th>Treatment Strategies for Mycosis Fungoides/Sézary Syndrome in Resource-Limited Settings</th>
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<tr>
<td>Stage</td>
<td>Treatment Options in Resource-Limited Settings</td>
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<tr>
<td>Early-stage (IA, IB, IIA)</td>
<td>First-line: • Topical corticosteroids • Heliotherapy • Radiation therapy</td>
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<td></td>
<td>Second-line: • Topical chemotherapy (mechlorethamine or carmustine) • Low-dose oral methotrexate</td>
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<tr>
<td>Advanced-stage (IIB, III, IV)</td>
<td>First-line: • Doxorubicin • Gemcitabine</td>
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<tr>
<td></td>
<td>Second-line: • Chlorambucil • Cyclophosphamide • Etoposide • High-dose methotrexate</td>
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<td></td>
<td>(consideration can be given to combining with topical therapies)</td>
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<tr>
<td>Large-cell transformation (if aggressive growth rate)</td>
<td>First-line: • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)</td>
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<tr>
<td></td>
<td>Second-line: • DHAP (dexamethasone, cytarabine, cisplatin) • GDP (gemcitabine, dexamethasone, cisplatin) • ICE (ifosfamide, carboplatin, etoposide) • Monotherapy: ifosfamide, gemcitabine</td>
</tr>
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</table>
Based on the consensus reached at the conference, this patient was treated with gemcitabine at 1000 mg/m² on days 1, 8, and 15 every 28 days, and showed a significant response after 2 cycles with minimal toxicities to date.

Conclusions

The incidence and economic burden of cancer in SSA is increasing, and innovative strategies are needed to improve care and cancer control in this population. This report proposes guidelines for the diagnosis and treatment of CTCL in resource-limited settings, and identifies areas for potential investigation to improve cancer care in this region.

References