# Research letter

## Management of advanced cutaneous T-cell lymphoma: role of the dermatologist in the multidisciplinary team

DOI: 10.1111/bjd.13849

Dear Editor, Non-Hodgkin lymphoma is a heterogeneous group of lymphoproliferative disorders[1] accounting for < 5% of cancers worldwide.[2] Mycosis fungoides (MF) and the leukaemic variant Sézary syndrome are the most common subtypes of cutaneous T-cell lymphoma (CTCL).[3] Early-stage MF is confined to the skin but may progress to cutaneous tumours/nodules and/or involve extracutaneous sites such as lymph nodes, blood or visceral organs.[4] Advanced-stage disease is associated with substantially reduced survival, with median overall survival of 4·7-1·4 years for patients with stage IIB–IVB disease.[5] However, the clinical course is unpredictable and disease progression varies widely, with some patients managing skin lesions for decades and others progressing more rapidly to advanced-stage disease.[6]

Although treatment of early-stage CTCL is often managed primarily by dermatologists, advanced disease is ideally treated by a multidisciplinary team of dermatologists, haematologists/oncologists and supporting team members, including radiation oncologists, primary-care doctors, nurses, social workers and nutritionists.[3] Due to the rarity and heterogeneity of the disease, difficulty in diagnosis and staging, and a variety of treatment options – including investigational therapies – patients should be referred to an academic or lymphoma specialty centre at the time of suspected CTCL. Routine tests, monitoring and administration of treatment can be performed locally; however, specialty centres should remain involved to help coordinate optimal care. In these cases, it is vital that dermatologists continue to work with community haematologists/oncologists to manage patients, even for those with advanced CTCL. Note that, in some countries (e.g. Germany, France), it is normal for dermatologists (oncodermatologists) to manage patients throughout the disease course of CTCL.

Visible skin changes in patients with CTCL may include patches, plaques, tumours and/or erythroderma; lesions are often seen first in nonsun-exposed areas of the body, but may appear elsewhere, and clinical presentation varies widely. The median age at diagnosis has been reported as 54 years,[5] but rates increase exponentially with age, and there is roughly a 1·5 : 1 male-to-female and black-to-white predominance.[7,8] Diagnosis of CTCL is often difficult because the clinical presentation and histology may resemble those of benign conditions, such as eczema, psoriasis or other inflammatory dermatoses, and it may initially respond to therapies used for these conditions (e.g. corticosteroids).[6,9] From the onset of symptoms to diagnosis, multiple biopsies over several years may be required, and a solid clinicopathological correlation is crucial, particularly in early-stage disease.[6,9,10] The histological criteria for diagnosis of early-stage disease developed by Guitart *et al.*[11] should be used as guidance. In addition, a point-based algorithm was developed that integrates clinical, histological, immunophenotypic and molecular criteria,[12] allowing for diagnosis to be made with less histological rigour than required by Guitart *et al.* Updated guidelines on staging and classification[4] and a consensus statement on clinical end points and response criteria have also been published;[13] both include assessments in the skin, lymph nodes, blood and viscera.[4,13]

Patients with advanced disease (stage ≥ IIB) typically receive systemic therapies (Table 1), with or without topical therapies,[3] under the care of a dermatologist comfortable with prescribing systemic therapies, or a haematologist/oncologist, and transitions from dermatologist to haematologist/oncologist care vary and are locally determined. Treatment goals in advanced CTCL include reducing the burden of disease (including management of pruritus), delaying progression and improving or preserving quality of life.

Dermatologists play an important role in guiding treatment decisions, even for systemic treatments in advanced CTCL. Dermatologists have unique expertise in the skin, making them most capable of providing skincare guidance and assessing and managing skin changes as they relate to disease, adverse events and responses to treatment. Moreover, dermatologists may have more experience in the use of certain systemic therapies (e.g. retinoids and low-dose methotrexate) than the treating haematologists/oncologists. Many patients with CTCL will require multiple therapies over the course of their disease, and durable responses in patients with advanced CTCL are difficult to achieve.[5] Thus, dermatologists can help minimize early termination of treatment by monitoring and responding to skin adverse events, as well as by differentiating disease progression from drug eruption or worsening appearance of lesions related to tumour cell death or radiation dermatitis.

The visible skin changes associated with CTCL impact patients both physically and emotionally. They may be disfiguring, affect everyday interactions, cause difficulty with use of hands or walking, and require daily care from patients and/or caregivers.[6] Dermatologists should formally measure the body surface area (BSA) involvement of disease (size of the patient's palm and fingers approximates 1% of BSA and can be used to

**Table 1** Systemic therapies recommended by the National Comprehensive Cancer Network (NCCN) for the treatment of patients with mycosis fungoides/Sézary syndrome[3]

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| Retinoids/rexinoids: bexarotene,[a] all-*trans*-retinoic acid, isotretinoin (13-*cis*-retinoic acid), acitretin |
| Interferons |
| Histone deacetylase inhibitors: romidepsin,[a] vorinostat[a] |
| Extracorporeal photopheresis[a] |
| Methotrexate |
| Brentuximab vedotin |
| Gemcitabine |
| Liposomal doxorubicin |
| Pralatrexate |
| Chlorambucil |
| Pentostatin |
| Etoposide |
| Cyclophosphamide |
| Temozolomide |
| Alemtuzumab |
| Additional regimens used to treat PTCL (see NCCN guidelines for PTCL for details) |

PTCL, peripheral T-cell lymphoma. [a]Agents with approval from the US Food and Drug Administration for patients with cutaneous T-cell lymphoma.

assess the amount of skin disease involvement), typically using the modified Severity Weighted Assessment Tool, in which patches, plaques and tumours are multiplied by a factor of 1, 2 and 3 or 4, respectively.[13] Rigorous assessment of skin involvement at baseline and throughout treatment is important because the extent of involvement is significantly associated with the risk of disease progression and survival.[14] Dermatologists are particularly capable of categorizing the nuanced changes in skin lesions during treatment to assess responses to therapy.

The majority of patients with CTCL experience pruritus (itching), even in early-stage disease.[6,15–17] Pruritus may cause difficulty with sleep or performance of daily activities,[6,15,16] may significantly impact quality of life,[15,16] and may be debilitating for some patients.[17] Relief of pruritus may be accomplished by targeting the itch directly or the cause of itch by inducing remission.[17] Pruritus associated with CTCL may respond to standard itch treatments (e.g. antihistamines, topical corticosteroids), but often the condition responds inadequately or not at all. Agents that target pathways involved in CTCL-associated pruritus include aprepitant, naloxone, naltrexone, butorphanol, mirtazapine, gabapentin and thalidomide.[17] Phototherapy-based treatments and extracorporeal photopheresis used to target the disease have also been shown to reduce pruritus in some patients. Some systemic therapies, including alemtuzumab, vorinostat and romidepsin, have shown variable efficacy in reducing pruritus.[18–20] An in-depth analysis of romidepsin demonstrated a clinically meaningful reduction of pruritus in 43% of patients with moderate-to-severe pruritus at baseline, including patients who did not achieve an objective response.[19] Alternatively, some topical therapies for CTCL may cause or exacerbate pruritus, including topical retinoids, carmustine and nitrogen mustard (mechlorethamine).[17] Because of their specific focus on eliminating cancer, haematologists/oncologists, when making treatment decisions, may minimize or overlook the impact that pruritus can have on a patient's quality of life.

As a result of compromised skin and poor immune function, patients with CTCL have a risk of infections; in particular, patients with erythroderma commonly experience *Staphylococcus aureus* infections.[6,21,22] Patients with advanced disease often die of infections.[21,23] Dermatologists should advise patients on prevention of infection by optimizing the skin barrier through proper skin moisturizing, bathing techniques, sun exposure, clothing, topical antibiotics and other such measures.[3,24] Additionally, routine bacterial decolonization of the skin can be done via diluted bleach baths/soaks. Patients with suspected/active infections are given topical and/or oral antibiotics.[3] Moreover, tumours and thicker plaques may break down and require wound care. Dermatologists can play a major beneficial role in coordinating this care.

Dermatologists, in conjunction with nurses, play a key role in patient and caregiver guidance regarding skincare and in the assessment and management of skin lesions or toxicities to reduce disease burden throughout the treatment of CTCL. Without guidance from dermatologists, haematologists/oncologists may discontinue therapies prematurely if the therapies appear to correlate worsening skin appearance with disease progression. However, worsening skin may be related to many other conditions, including manageable adverse events, drug eruption or rapid exfoliative response to treatment; patients should continue on therapy when there is clinical benefit.

In conclusion, patients with advanced-stage CTCL are best served under the care of a multidisciplinary team of dermatologists (Table 2), haematologists/oncologists and supporting staff. All patients with suspected CTCL should be referred to an academic or specialty centre with expertise in CTCL. For patients managed in a community setting, whenever possible, community providers should partner with specialty centres for ongoing guidance. Additionally, although some dermatologists may believe that their role is mainly in diagnosing and treating early-stage CTCL, it is crucial that dermatologists remain

**Table 2** Key roles for dermatologists on the multidisciplinary team for the treatment of patients with cutaneous T-cell lymphoma (CTCL)

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| Knowledge of current topical and systemic therapies for CTCL to provide recommendations |
| Knowledge and use of TNMB classification and staging system |
| Performance of frequent skin examinations (including establishment of mSWAT scores) to monitor response to treatments and toxicities |
| Evaluation and treatment of pruritus |
| Evaluation and treatment of skin infections and colonization |
| Coordination of and recommendations for wound care |

TNMB, tumour, lymph node, visceral organs, peripheral blood; mSWAT, modified Severity Weighted Assessment Tool.

involved in advanced disease due to their unique expertise in the skin.

## Acknowledgments

The authors take full responsibility for the content of this manuscript but thank Stacey Rose, PhD (MediTech Media), for providing medical editorial assistance, which was supported financially by Celgene Corporation.

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Funding sources: B.P. was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases grant K08 AR055986 and the James P. Wilmot Cancer Center Fellowship. C.Q. was supported by the Ted Schwartz Family Foundation.

Conflicts of interest: B.P. is a consultant and speaker for Celgene Corporation. C.Q. has served as an advisor for Celgene Corporation.