Cutaneous T-cell lymphoma: A spectrum of disease and treatments

HOT SPOT

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General overview

- Cutaneous T-cell lymphomas (CTCLs) are a rare group of non-Hodgkin's lymphomas (NHLs) characterized by malignant T-cells infiltrating the skin. Mycosis fungoides (MF) is the most common form (about 75% of CTCL cases) and is seen as a more indolent disease. Sézary syndrome (SS) is more aggressive and includes both blood and skin involvement.
- There are 50 known skin manifestations of CTCL. MF generally presents with asymptomatic scaly patches. Plaques, cutaneous tumours, ulcerations or fissuring of the skin can occur.
- SS presents with severe involvement of most of the skin, and intense, relentless itch. Malignant T-cells are found in the circulation. Internal involvement of lymph nodes, lung and solid organs is rarely seen.
- A diagnosis of CTCL is based on clinical-pathologic correlation. Repeated biopsies of multiple affected areas may be necessary, but characteristic malignant T-cells are typically found in the epidermis and dermis of the skin. In early-stage disease, diagnosis may be based on immunophenotypic features of the T-cells; a higher presence of immature cells is strongly indicative of lymphoma.
- Advanced SS is defined by the presence of erythroderma, generalized lymphadenopathy and malignant T-cells (Sézary cells) in skin, lymph nodes and peripheral blood. The degree of peripheral blood involvement required to make a diagnosis is commonly 1×10^9/L or 5% Sézary cells. Additionally, a CD4:CD8 ratio greater than 10 with the presence of a clonal population of CD4 cells is sometimes thought to be a better method of determining peripheral blood involvement.
- According to a recent review of the Surveillance Epidemiology and End Results (SEER) database and other registries, the incidence of CTCL is on the rise (Criscione, 2007). It is further estimated that 7,500 Canadians are diagnosed with NHL each year, approximately 4% of which are CTCL (CCS, 2010; Lansigan, 2010).

Classification

- Several disease subtypes make up the broad spectrum of CTCL (Piliotis, 2007).
- Less common forms include a number of MF variants. **Folliculotropic** MF is characterized by the presence of folliculotropic infiltrates with sparing of the epidermis, mucinous degeneration of hair follicles and preferential involvement of the head and neck. **Pagetoid reticulosis** is characterized by localized patches or plaques with an intraepidermal proliferation of neoplastic T-cells. **Granulomatous slack skin** is typified by the development of pendulous folds of atrophic skin, generally involving the axilla or groin.
- **CD30+ lymphomas** include anaplastic large-cell lymphoma of the skin, consisting of larger tumour cells, and lymphomatoid papulosis, a chronic, recurring and potentially self-healing skin disorder that histologically resembles lymphoma.
- Peripheral T-cell lymphomas, panniculitic T-cell lymphoma and natural killer/T-cell lymphomas of the skin are all rare and **highly aggressive forms** of CTCL largely involving distinct subset of T-cells.

Staging

- The staging of CTCL provides both prognostic value and assistance in management decisions. The most commonly used staging system is based upon a tumour-node-metastasis-blood (TNMB) classification that has been modified by the International Society for Cutaneous Lymphomas/EORTC (Table 1).
- Prognosis varies substantially with disease stage (Lansigan, 2010).
  - Patients with patch-plaque disease at earlier stages (IA, IB and IIA) have an expected survival of >12 years; stage 1A patients have a survival very similar to age-matched controls
  - Patients with tumours or erythroderma at stages IIB and III have a median survival of approximately 4 years
  - Late-stage patients (stage IV) with lymph node or visceral involvement and SS patients have a median survival <3 years.
- Many patients develop fatal infections as complications due to the immunosuppressive effects of systemic therapy, as well as their own impaired immunity and chronic loss of skin integrity. The malignant T-cells expand at the expense of normal T-cells, resulting in reductions of functional T-cells, the production of T helper (Th)-1 type cytokines, and natural killer cell activity.

Treatment

- Many treatment options are available to treat CTCL patients, though few are potentially curative. As such, patients often experience many treatment modalities in the course of managing their disease, including both skin-directed and systemic therapies.
- Skin-directed therapy is used more frequently in earlier stages and systemic therapy is typically used to treat aggressive or advanced disease.
- Recent efforts have led to the development of novel biological and molecular targeted therapies. Systemic chemotherapy and stem cell transplantation can be used when most other viable options have been exhausted. Traditional chemotherapy (e.g., CHOP) is generally delayed because of the minimal, transient benefits that come at the cost of significant toxicity.
- Disease stage dictates prognosis and the choice of specific treatment in CTCL (Table 2). Early-stage MF patients often respond to skin-directed therapies (SDTs) alone, but

Table 1. TNMB staging system for CTCL as modified by the International Society for Cutaneous Lymphoma/European Organisation for Research and Treatment of Cancer. T: tumour, N: nodes, M: metastases, B: blood (Adapted from: Lansigan, 2010).

TNMB STAGING SYSTEM		T1: Limited patch/plaque	T2: Generalized patch/plaque	T3: Tumour	T4: Erythroderma
N0: Nodes uninvolved	M0	IA	IB	IIB	IIIA
N1: Nodes enlarged and uninvolved	M0	IIA			IIIB
N2: Nodes normal and involved	M0	IVA			
N3: Nodes enlarged and involved	M0				
N0–N3: Visceral organs involved	M1	IVB			
B0: No significant peripheral blood Sézary cells					
B1: low tumour burden; <1000/μL Sézary cells					
B2: high tumour burden; >1000/μL Sézary cells					

Table 2. CTCL treatment options as determined by stage (Adapted from: Lansigan, 2010).

Stage	Initial disease treatment	Relapsed/refractory disease treatment
IA	Skin-directed therapy	Additional skin-directed therapy ± single-agent therapy
IB/IIA	Skin-directed therapy ± single-agent therapy	Additional skin-directed therapy + single-agent therapy
IIB	Skin-directed therapy + single-agent therapy	Additional skin-directed therapy + single-agent therapy OR multi-agent therapy OR allogenic SCT
IIIA/IIIB	Skin-directed therapy ± ECP	Multi-agent therapy OR allogenic SCT
IVA/IVB	Chemotherapy OR multi-agent therapy	Chemotherapy OR allogenic SCT

Skin-directed therapy: Topical steroids, topical retinoids, topical chemotherapy, photodynamic/UV therapy and electron beam therapy; **Single-agent therapy:** HDAC inhibitors, monoclonal antibodies, immune-targeted therapies; **ECP:** Extracorporeal photopheresis; **Chemotherapy:** Traditional systemic chemotherapy; **Multi-agent therapy:** Combinations of skin-directed therapies, single-agent therapies, and/or chemotherapies

patients with extensive or refractory disease often require more aggressive single-agent therapies, often combined with skin-directed therapy and/or systemic therapies (Akilov, 2011; Gardner, 2009; Lansigan, 2010; Piliotis, 2007).

Skin-directed therapies

Earlier stage disease is commonly treated with one or more skin-directed therapies (Akilov, 2011; Gardner, 2009; Lansigan, 2010; Piliotis, 2007).

- Topical corticosteroids: Effective in minimally symptomatic and patch-stage disease, response rates greater than 90% and complete remission rates of more than 60% have been reported for early-stage patients. High potency preparations such as clobetasol propionate 0.05% are recommended as they are toxic to the causal T-cells. Milder corticosteroids or topical calcineurin inhibitors are less desirable since they may decrease autoimmunity locally and not treat the disease.
- Topical retinoids: Topical Targretin® (bexarotene) can achieve response rates of 50% in early stage disease, but is not available in most provinces. Retinoids (topical or oral) can act synergistically with light therapy. In Canada, Tazorac® (topical tazarotene) and topical tretinoin are available and are alternatives to bexarotene (which is not available).
- Topical imiquimod: Originally formulated for the treatment of genital warts, topical Aldara® has also been effective in several skin malignancies, including CTCL, due at least in part to its induction of localized interferon (IFN)-α.
- Topical chemotherapy: Although no longer widely available, nitrogen mustard has been used topically since 1959 and may yield response rates of up to 80%. The mechanism of action for topical nitrogen mustard remains unclear, as it seems to be independent of the alkylating properties. Allergic reaction and contact dermatitis are common risks. Topical BCNU (carmustine) had been used with mixed results, but is now rarely used.
- Phototherapy: Two forms of phototherapy are in common use—Psoralen (either oral or bath) and ultraviolet A irradiation (PUVA), and narrowband ultraviolet B (NB-UVB). Response rates of up to 70% have been seen with PUVA for MF. PUVA is initiated at two sessions per week and the usual course of therapy is expected to be at least three months. In white patients, more than 200 PUVA treatments is associated with an increased risk of secondary skin cancers. NB-UVB may be equally effective to PUVA and does not require psoralen. NB-UVB is usually initiated three times per week and will also take at least three months of therapy. Skin cancer risks are not a major concern with NB-UVB and there is no known limit on exposures.
- Electron beam therapy: In early stage CTCL, electron beam therapy can be used as a single modality. However, it is commonly combined with other modalities for more advanced disease. Resistant local disease can be very effectively treated with radiotherapy.
- Total skin electron beam radiation (TSEB): A more aggressive method of administering radiation for CTCL patients with advanced disease. TSEB therapy is often challenging for patients and associated with major long-term cutaneous side effects such as complete hair loss, dry skin, and thyroid failure. TSEB is typically reserved for patients with resistant tumours or SS. TSEB can work well in combination with systemic therapies.

Systemic therapies

Advanced stage disease is commonly treated with one or more systemic therapies, which may also be combined with skin-directed therapies (Akilov, 2011; Gardner, 2009; Lansigan, 2010; Piliotis, 2007). Combination therapy is often the most effective approach.

- Extracorporeal photopheresis (ECP): Photopheresis is a process in which white blood cells are treated with 8-methoxypsoralen, which is activated by exposure to UV light using a pheresis device. The procedure is generally repeated either biweekly or monthly and can take months to yield a response. The published data consist mostly of small trials reporting response rates between 33% and 88%. ECP is mostly effective for late-stage CTCL, especially where there are circulating Sézary cells and when used in combination with systemic therapy. ECP is now funded by the MOHLTC and available via Princess Margaret Hospital.
- Histone deacetylase (HDAC) inhibitors: Targeting the epigenetic regulation of gene expression, HDAC inhibitors are a new class of agents that decrease histone binding to DNA and allow for chromatin expansion and increased transcription of a subset of genes. Vorinostat® (suberoylanilide hydroxamic acid) was demonstrated to be effective clinically in the treatment of CTCL with overall response rate of 36% in patients who had received an average of 3.5 prior therapies. Istodax® (romidepsin) is a more recent selective HDAC inhibitor that has been shown to have similar response rates and toxicities to Vorinostat®. Side effects include an increase in thromboembolic events.
- Monoclonal antibodies: Campath® (alemtuzumab) is a monoclonal antibody that targets CD52, an antigen expressed on mature lymphocytes. It has been shown to be effective in several types of lymphomas, including CTCL. Overall response rates in clinical trials have been variable (30% to 85%). However, most responses are relatively brief. Because of a significant toxicity profile, Campath® may have a more defined role when administered as low-dose, intermittent subcutaneous therapy.
- Immune-targeted therapy: As a disease of malignant immune cells, CTCL has been targeted with immunotherapy for many years. IFN-α has been shown to have significant activity in treating CTCL, though a wide range of toxicities have also been observed. More recently, IFN-γ and recombinant human interleukin (IL)-12 have demonstrated some degree of early success in treating CTCL, as additional modulators of the immune system. Denileukin difitox is a fusion protein toxin that targets IL-2 receptor positive cells. Trials have indicated durable responses in between 30% and 46% of CTCL patients of both early and late stages. Side effects of denileukin difitox are variable, but the more serious ones include hypersensitivity-mediated infusion reactions and manifestations of mild capillary leak syndrome.
- Oral retinoids: Consist of vitamin A-derived compounds that are physiological regulators of many processes. First line in Canada is typically isotretinoin (Accutane® or Clarus®), a traditional retinoid with response rates of 40% to 70% in limited stage disease. Possible side effects include teratogenicity, hyperlipidemia, headache, personality changes, dryness of the skin and mucous membranes, fatigue, arthralgias and bone changes.
- Systemic chemotherapy: Oral alkylator, antimetabolite, purine analog, and anthracycline regimens have all been used in the treatment of CTCL. Many small-scale studies have reported response rates ranging from 18% to 100%, but most responses are transient. Furthermore, extensive side effects relegate systemic chemotherapy to patients with advanced disease that has become refractory to all other options. More recently, Revlimid® (lenalidomide) and Velcade® (bortezomib) have been reported to yield durable responses. While Velcade® was better tolerated in these early studies, both novel agents demonstrate promise.
- Stem cell transplantation (SCT): While autologous SCT has shown mixed results, advanced, refractory CTCL has been shown to respond to allogeneic SCT with durable remission. Allogenic SCT provides an advantageous immune-mediated graft-versus-tumour (GvT) response that appears to account for most of the success of the procedure. Optimal conditioning regimens for allogeneic SCT in CTCL have not yet been defined and, as CTCL tends to affect older adults, certain myeloablative regimens may result in higher morbidity and mortality.

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References

Available upon request.

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