Cutaneous T-Cell Lymphoma: Pathogenesis and Treatment

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The article by Drs. Girardi and Edelson is an extensive review of the history, diagnosis, and current management of cutaneous T-cell lymphoma (CTCL). This entity is classified in the Revised European-American Lymphoma/World Health Organization (REAL/WHO) classification system as mycosis fungoides and Sézary syndrome.[1] However, CTCL has been used as an umbrella term for several different clinical variants of this syndrome. A careful evaluation of the patient with a suspicious lesion and the early use of T-cell receptor gene rearrangements for diagnostic purposes is important.

Clinical Variants of CTCL
Drs. Girardi and Edelson discuss the major variants of CTCL in detail. The most common presentation would be classic patch/plaque CTCL, which presents with single or multiple erythematous patches or plaques. These lesions typically originate in non-sun-exposed areas, then slowly progress. These patients often go undiagnosed for years, and multiple skin biopsies may be necessary before a histologically based diagnosis can be obtained.

Variants of the patch/plaque CTCL include hypopigmented disease (seen in dark-skinned patients), poikilodermatous patch/plaque CTCL (a slow-growing, chronic, solitary lesion), and alopecia mucinosa (which presents with clusters of erythematous papules associated with hair loss). All of these variants progress very slowly over a number of years and may require numerous biopsies for diagnosis.

Tumor-stage CTCL may develop in a patient with prior patch/plaque-stage disease or de novo. Patients can also have CTCL that transforms to a more aggressive, diffuse, large-cell lymphoma in this clinical situation. Therefore, in order to properly direct therapy, a new biopsy is often recommended when this condition presents. If the CTCL has transformed to a diffuse, large-cell lymphoma, the patient usually will not benefit from topical therapies and will require systemic chemotherapy.

In erythrodermic CTCL, patients present with bright red cutaneous erythema that usually appears de novo but occasionally arises from established patch/plaque-stage disease. This form of the disease is associated with a median life expectancy of only 1.5 to 2 years[1] is much more aggressive than other types of CTCL. This form of CTCL usually necessitates systemic therapy, such as extracorporeal photopheresis, interferon therapy, chemotherapy, or antibody therapy.

Hematopathology of Cutaneous T-Cell Lymphoma
The authors also discuss non-patch/plaque CTCL syndromes. However, it may be clearer to describe these conditions according to the most current REAL/WHO classification system.[1] In this system, mycosis fungoides and Sézary syndrome are the two entities that usually fall under the name of CTCL. The entities known as CD30-positive and CD30-negative T-cell lymphomas, are most often called anaplastic large-cell (T/null-cell) lymphomas. These lymphomas can present as primary cutaneous lymphomas[2] (for which radiation therapy is typically used) or as systemic disease[3] (which must be treated with systemic chemotherapy).

Cutaneous T-cell lymphoma should also be differentiated from peripheral T-cell lymphomas, which often have a mixture of small and large cells. Like aggressive lymphomas, peripheral T-cell lymphomas need to be treated with chemotherapy, but often have a poorer prognosis than their B-cell lymphoma counterparts.[4]

Skin-Directed Therapy
First-line therapy for patients with limited CTCL is typically phototherapy with psoralen plus ultraviolet A light (PUVA) or topical nitrogen mustard.[5,6] Intermittent or continuous use of these therapies can often control the disease for years. However, many physicians recommend total-skin electron-beam irradiation for patients with limited-stage disease, as it appears to be curative in a
Systemic Therapy

Once the patient presents with more advanced disease, systemic therapy is needed. Extracorporeal photopheresis has demonstrated some benefit in patients with Sézary syndrome.[8] The addition of methotrexate or interferon therapy may also improve responses in some patients. Oral bexarotene (Targretin) is a retinoic X receptor (RXR)-specific retinoid that has demonstrated efficacy in CTCL.[9] In some patients, this may be an alternative with few toxicities other than hyperlipidemia and hypothyroidism.

Another new agent against this disease is DAB389IL-2 (Ontak), which is a portion of the diphtheria toxin conjugated to interleukin-2.[10] This therapy demonstrated some responses in patients with CTCL who had failed many other therapies. However, problems associated with this drug include capillary leak syndromes, hypotension, and pulmonary edema.

Another therapy that was not discussed at length in the article is interferon-alfa, which is quite useful in some patients with extensive CTCL or erythrodermic-phase Sézary syndrome. Typically, a low dose, such as 3 million units three times per week, needs to be initiated. Then, as tolerated, the dose can be gradually increased over a number of months. The overall response rate for interferon appears to be about 55%, with a 15% to 20% complete response rate.[11]

Systemic chemotherapy can also sometimes induce a partial response in CTCL patients[]at least temporarily. Routine chemotherapies, such as CHOP (cyclophosphamide, doxorubicin HCl, Oncovin [vincristine], and prednisone), which are useful for aggressive lymphomas, usually do not produce long-term results in patients with CTCL. More useful agents in this setting are the purine analogs, such as cladribine (2-CdA [Leustatin]) and fludarabine (Fludara).[12]

In a trial of 2-CdA administered to multiply relapsed CTCL patients, the overall response rate was 47%, and complete responses occurred in 3 (20%) of 15 patients.[12] A trial of fludarabine and interferon by Kuzel et al showed a 62% complete response rate, 28% partial response rate, and a median duration of response of 28 months.[13]

Conclusions

In summary, future agents currently in clinical trials and under consideration include antibodies against the T-cell receptor that are unconjugated, radiolabeled, or conjugated with toxins. It may also be possible to use the patient's T-cell receptor abnormality from his or her lymphoma in a vaccine protocol similar to how the idiotype vaccines are used in B-cell lymphomas. Combination therapy will most likely be needed to obtain the best antilymphoma effects for patients with CTCL.

References:


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