Diagnosis and Treatment of Sézary Syndrome
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Citation

Abstract
Sézary syndrome (SS) is the leukemic variant of Mycosis fungoides, the most common form of cutaneous T-cell lymphoma (CTCL). The classic triad of exfoliative erythroderma, lymphadenopathy, and pruritis plus increased numbers of atypical lymphocytes on the blood smear are characteristic of SS. Early diagnosis is often missed in the elderly whose symptoms of dry skin and itching are attributed to advanced age. Histopathology, flow cytometry, and attention to the patient's symptoms allows early detection of SS and institution of combined immunomodulatory therapy. Combined immunomodulatory therapy is more effective, less immunosuppressive, and of longer duration than chemotherapeutic options currently available for Sézary syndrome. Skin directed palliative care is an important adjuvant for managing the symptoms of Sézary syndrome. This includes treating the very common Staphylococcus aureus skin colonization to improve erythroderma and liberal use of topical corticosteroids in lieu of oral steroids. Reports of long-term remissions have been reported with allogeneic stem cell transplantation, but a complete cure is rare.

BACKGROUND
Cutaneous T-cell lymphoma (CTCL) includes all the variants of T-cell mediated lymphomas presenting in skin. In 1975, Edelson first proposed that mycosis fungoides (MF), Sézary syndrome (SS), and related neoplasms be designated under the broader classification of cutaneous T-cell lymphomas (CTCL). The clinical and histologic features may overlap between MF and SS and one may evolve from the other. Cutaneous T-cell lymphoma variants that are defined by their clinical presentation and immunohistochemistry makers are less common. These include anaplastic large cell lymphoma, subcutaneous panniculitic T-cell lymphoma, peripheral T-cell lymphoma, CD30- lymphoma, and natural killer T-cell lymphoma.

The most common of the cutaneous lymphomas is mycosis fungoides and its leukemic variant, Sézary syndrome. CTCL has an incidence rate of 0.45 per 100,000 person-years. MF comprises 85% and SS about 15% of the total MF/SS population. Overall median survival of SS is less than three years from time of diagnosis. Although with early diagnosis and treatment, extended survival times are possible. Also, with early diagnosis, improved treatment responses are more likely. Mycosis fungoides is staged using a specific TNM system from IA to IVB, based on extent of cutaneous involvement (T stage), lymph node, blood and visceral involvement. Sézary syndrome (SS) may evolve from mycosis fungoides or present de novo as a separate disease entity in the CTCL classification. The original MF staging system did not take into account quantitative staging of the blood, which is now available through use of flow cytometry. Currently available tools for evaluating lymphoid infiltrates include molecular diagnostics, flow cytometry, and immunohistochemistry tests; however, none is perfect and no single attribute mandates a specific diagnosis without incorporating all available clinical, pathologic, immunohistochemical, and cytogenetic findings. Even with the wealth of available medical information and studies, a definitive histopathologic diagnosis of MF or SS can be elusive with overlap between low-grade lymphoma and reactive infiltrates. Lack of experience because of the rarity of some lymphomas may also be a problem. This article will explore the clinical manifestations of early and late Sézary syndrome and review skin directed palliative care and treatment options.

CLINICAL DIAGNOSIS
Classic Sézary syndrome symptoms are exfoliative erythroderma, lymphadenopathy, and pruritis with the presence of Sézary cells, large lymphocytes with a cerebriform nucleus, on peripheral blood smear. The appearance of clinical features of SS developing de novo without prior MF and within a short time interval is definitive of “classic SS”. Winkelmann et al also defined
pre-Sézary syndrome as the clinical findings of SS with circulating Sézary cells of less than 1,000 cells/mm.

Defining how best to quantitate SS cells and to define the number required for a diagnosis of SS has been the subject of controversy over the past 15 years.

Early diagnoses of SS are often missed by primary care physicians who are not knowledgeable about the subtle presenting signs of this disease. This includes patients diagnosed with adult-onset recalcitrant eczema who really have mycosis fungoides rather than dermatitis. Elderly persons with pruritis and xerosis may have SS and only over several years may develop exfoliative erythroderma required for the diagnosis of SS. The diagnosis is often missed because the patient's symptoms are attributed to age and dry skin. A biopsy at this point will most likely reveal atypical perivascular lymphoid infiltrate rather than epidermotropism required for MF.

Sézary patients often present with generalized exfoliative erythroderma, pruritus, and usually lymphadenopathy (Figure 1A). They may also present with dermatitis or infiltrating skin lesions and the latter form usually leads rapidly to erythroderma. Erythema can vary significantly due to body temperature and Staphylococcus aureus coloniziation. Palmoplantar keratoderma are often present on acral skin surfaces and may coexist with a dermatophyte infection (Figure 1B). Fissures on top of the keratoderma may be infected with S. aureus or beta hemolytic streptococcus. Patients complain of intense pruritis that can prohibit sleep. Affected individuals complain of cold intolerance due to excessive skin flaking. Cutaneous tumors may also be present. Ectropion is commonly seen, especially in later stages of disease. Nails are often affected and become brittle and dystrophic. Alopecia is frequently observed in many SS patients any may present as diffuse alopecia, alopecia areata, follicular mucinosis or alopecia totalis or universalis. Sézary syndrome patients represent a subset of MF with leukemia and consequently may also have patches, plaques and tumors.

DIFFERENTIAL DIAGNOSIS
The differential for exfoliative erythroderma of Sézary syndrome includes cutaneous drug reactions, actinic reticuloid, drug-induced pseudolymphoma reactions, severe eczematous reactions, psoriasis, severe seborrheic dermatitis, parapsoriasis, and pityriasis rubra pilaris and photosensitivity conditions (i.e. lupus, dermatomyositis).

HISTOPATHOLOGY
The key to early diagnosis of SS is clinical suspicion and awareness of subtle clues on histopathology. Skin specimens
Diagnosis and Treatment of Sézary Syndrome

from primary de novo SS patients do not show epidermotropism or Pautrier’s microabscesses but rather have perivascular collections of atypical cells with cerebriform nuclei (Figure 2).\textsuperscript{11} Biopsy specimens are considered diagnostic in only 60% of all cases of CTCL and SS.\textsuperscript{12} Crush artifact may obscure diagnosis because lymphoid infiltrates are particularly fragile.\textsuperscript{8} Perivascular lymphoid infiltrate is often seen on punch biopsies and signifies disease migration to blood. This finding should be regarded as highly suspicious for Sèzary syndrome in a patient with any of the clinical signs or symptoms. In contrast to mycosis fungoides, epidermotropism frequently is lacking in SS; however, abnormal perivascular lymphocytes are present.\textsuperscript{13} Pautrier’s microabscesses, which are pathognomonic of mycosis fungoides, are rare in SS specimens unless it evolved from pre-existing MF.\textsuperscript{14} Perivascular lymphoid infiltrates with abnormal lymphocytes are present in SS.

**Figure 3**
Figure 2: Skin biopsy from Sèzary Syndrome. There is a dense perivascular and superficial dermal atypical lymphoid infiltrate with minimal focal epidermotropism.

**LABORATORY STUDIES**

A complete blood count (CBC) with differential could be helpful in diagnosing early SS, especially if a manual differential is performed. Lymphocytosis, monocytosis, and/or eosinophilia can be present on routine differential. Sèzary cells which are large activated T-cell lymphocytes have a lobular, convoluted “cerebriform” nucleus and are seen on peripheral smear (Figure 3).\textsuperscript{15} These cells are generally counted as mononuclear cells by an automated blood analyzer and thus monocytosis should raise the question of SS. A Sèzary cell count of 20% or >1000 cells/m\(^3\) has been proposed as diagnostic of SS,\textsuperscript{16} however, flow cytometry may replace this technique in the future.

**Figure 4**
Figure 3: Blood smear from patient with Sèzary syndrome. A mixed population of small and large tumor lymphocytes with cerebriform nuclear morphology are noted (arrow on typical Sèzary cell). Eosinophilia (top cell) is also frequently present in Sezary Syndrome and may contribute to the pruritus and atopy.

Flow cytometry is a more exact method for detecting a population of aberrant T cell clones in the blood. In patients with SS, loss of markers for CD26, and less frequently CD7, are usually present on CD4+ SS lymphoma cells. The number of CD4+CD26- cells should be less than 30%. If there are increased numbers of CD4+ cells or CD4+CD26- cells, SS should be considered. An increase in CD4+CD26- cells (>30%) is also shown to be a reliable way to follow the Sèzary count using flow cytometry.\textsuperscript{17} Decreased or absent expression of pan-T-cell antigens (CD2, CD3, CD5), absent expression of subset antigens (CD4-, CD8-, CD7-, CD26), or coexpression of T-cell antigens (CD4+, CD8+) is seen in SS.
and is indicative of a malignant T-cell population with aberrant antigen expression.\textsuperscript{14} In a review by Martí et al, 75% of cells were positive for the T-cell antigen CD45R0 and 65% expressed CD43.\textsuperscript{19} Expression of CD7 is deficient on circulating malignant T cells in about 60% to 70% of SS cases\textsuperscript{20} although in our experience, loss of CD7 is only seen in 26%\textsuperscript{-23}. This criterion has a high specificity for CTCL\textsuperscript{-22}. A CD4+/CD8+ ratio over 10 is highly suspicious of SS in the blood.\textsuperscript{4} Immunophenotyping in the past demonstrated surface markers on cells but did not distinguish between benign and malignant cells.\textsuperscript{23} However, use of two markers and colors can distinguish loss of CD26 on CD4+ T-cells and discriminate between normal cells and tumor cells.\textsuperscript{17}

**SURROGATE MARKERS**

There are some laboratory values that may be of benefit for detection of advanced lymphoma or for monitoring response to cancer therapy in SS. Beta-2-microglobulin (B2MG) co-associates to class I HLA antigens present on the surface of most nucleated cells. Serum levels of B2MG are increased in autoimmune diseases, viral infections (such as HIV) and lymphoproliferative syndromes and other neoplasms.\textsuperscript{19} Serum lactate dehydrogenase (LDH) is an index of biologic activity in several lymphomas, including MF/SS, and specifically can be elevated in the setting of large cell transformation of MF.\textsuperscript{19} Both beta-2-microglobulin and LDH can be monitored for management and prognosis of CTCL.\textsuperscript{24} T-cell growth factor (IL-2) is expressed on activated T-cells and can be measured in the circulation. Soluble interleukin 2 receptor (SIL2-R) is increased in almost all SS patients' sera and has been reported to correlate with erythroderma and with response to therapy.

**MOLECULAR DIAGNOSTICS**

Understanding the pathogenesis of CTCL has been advanced using molecular biology. Each T-cell undergoes a unique rearrangement of its T-cell receptor gene during T-cell differentiation and can serve as a molecular signature for identification of T-cell clones. Rearrangements can be detected by either Southern blotting (with a sensitivity of >10% of all T-cells) or by using the polymerase chain reaction and gradient gel electrophoresis (with a sensitivity of 1%). Clonality studies at the present time amplify the T-cell gamma gene by PCR with a band detected by a gradient gel electrophoresis. The caveat is that T-cell receptor gene rearrangements are not unique to or diagnostic of CTCL as they may be detected if too few cells are present in the infiltrate or in the setting of benign inflammatory diseases.

Diseases reported to have a T-cell clone detected in some cases include lichen planus, alopecia areata, lichen sclerosis et atrophicus, pityriasis lichenoides, pigmented purpuras, and clonal contact dermatitis.

Although inflammatory skin diseases generally display polyclonal T-cell gene rearrangements, the same can be said for cases of early mycosis fungoides, and even patients with SS can have several clones detected using more sensitive methods. Detection of a T-cell receptor gene rearrangement may be supportive for early diagnosis in a patient whose lymphoma fails to exhibit the clinical or histologic criteria.\textsuperscript{-23} When we studied the T-cell repertoire of SS blood for T-cell gene families, many patients showed several T-cell clones present.\textsuperscript{-24} However, of much interest was the finding of the presence of staphylococcal superantigens and TSST-1 (toxic shock related Staphylococcus) from skin and blood in patients and that the TCR V beta usage expected, i.e. Vb2 with TSST-1 was present.

In a second study using V gamma gene rearrangements to detect the size of the bands by DNA sequencing we found that patients' whose T-cell rearrangements were the same sized band in several lesions or several locations over time were most likely to progress and therefore were helpful in determining the diagnosis of MF/SS. Patients with several clones present in their skin or different clones in separate locations did not progress and had chronic skin lesions over a long period of time.\textsuperscript{-23} Thus, we demonstrated that finding a distinct sized T-cell receptor gamma band of a specific size in multiple skin lesions, nodes, or blood over time should be a helpful diagnostic tool to predict who will most likely to progress. In early stage patients, it may be useful to obtain skin biopsies in several anatomic locations for detection of a common clone. Demonstration of an identical clonal gene rearrangement in multiple biopsy specimens at the time of diagnosis can help predict patients who will show clinical progression.\textsuperscript{-26} In the future we can expect that DNA profiling will be useful to define a signature of gene expression that may distinguish SS from MF and other forms of CTCL.

**STAGING**

The TNMB (Tumor, Node, Metastasis, Blood) classification system is used for clinical staging of MF/SS CTCL patients (Table I).\textsuperscript{22, 27} According to this system, the erythroderma in Sézary patients classifies them as T4 (erythrodermic) with their blood or B2 (>1000 cells/mL). SS patients can have variable N (nodal involvement) and M (with or without visceral involvement, with bone marrow involvement judged
as M1). Since some patients arise de novo and others arise in the setting of prior MF, there is a lot of confusion with regard to staging SS patients. The initial stage at the time of histologic diagnosis is the “stage of the patient” for purpose of prognosis, although patients do progress to later stages over time.

**Figure 5**

Table I 26: TNMB Classification System for CTCL

<table>
<thead>
<tr>
<th>T</th>
<th>Subcategory</th>
</tr>
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<tbody>
<tr>
<td>T0</td>
<td>Histologically normal</td>
</tr>
<tr>
<td>T1</td>
<td>Limited patch/plaque (≤10% body surface area)</td>
</tr>
<tr>
<td>T2</td>
<td>Generalized patch/plaque (&gt;10% body surface area)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumors</td>
</tr>
<tr>
<td>T4</td>
<td>Erythroderma</td>
</tr>
</tbody>
</table>

N: Lymph nodes clinically uninvolved
H0: Lymph nodes enlarged, histologically uninvolved (eg, reactive)
H1: Lymph nodes clinically uninvolved, histologically involved
H2: Lymph nodes enlarged and histologically involved
M1: Visceral involvement
M0: No visceral involvement

Table II 8: Recommended Definitions for Subsets of Erythrodermic CTCL

<table>
<thead>
<tr>
<th>Subset</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>Rarely</td>
</tr>
<tr>
<td>Erythrodermic MF</td>
<td>Absent or minimal</td>
</tr>
<tr>
<td>E-CTCL NOS</td>
<td>Absent or minimal</td>
</tr>
</tbody>
</table>

The International Society for Cutaneous Lymphomas (ISCL) lists the recommended definitions for subsets of erythrodermic CTCL in Table II. The differences between SS, erythrodermic MF, and erythrodermic CTCL are delineated based on degree of erythroderma and on amount of blood involvement. Distinguishing between B1 and B2 classifications was recommended and will be studied to see if there is an effect on prognosis. A revised B1 blood rating would be defined as Sèzary cell count of <1000 cells/m³ or less than 20%, B2 blood rating (ie. Sèzary syndrome) would be >1000 cells/m³ or greater than 20% atypical T cells on peripheral smear.

Of interest, the number of atypical T-cells on smear may vary considerably from one day to another and be significantly increased in the setting of staphylococcus infections or sepsis.

**Figure 6**

Table II 8: Recommended Definitions for Subsets of Erythrodermic CTCL

<table>
<thead>
<tr>
<th>Erythrodermic CTCL (E-CTCL) subset</th>
<th>Pre-existing MF</th>
<th>Blood findings</th>
<th>T/K/N designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>Rarely</td>
<td>Leukemic</td>
<td>T/K/N: X B1* M8*</td>
</tr>
<tr>
<td>Erythrodermic MF</td>
<td>Absent</td>
<td>Absent or minimal</td>
<td>T/K/N: B1* M8*</td>
</tr>
<tr>
<td>E-CTCL NOS</td>
<td>Absent</td>
<td>Absent or minimal</td>
<td>T/K/N: B1* M8*</td>
</tr>
</tbody>
</table>

NOS, Not otherwise specified*B1 blood rating assigned for 20% or more atypical convoluted Sèzary cells per 100 lymphocytes on blood smears. B2 blood rating includes an absolute Sèzary count of 1000 cells/mm³ or more; a CD4/CD8 ratio of 10 or more due to an increase in CD3+ or CD4+ cells by flow cytometry; aberrant expression of pan-T-cell markers (CD2, CD3, CD4, CD5) by flow cytometry; increased lymphocyte counts with evidence of a T-cell clone in the blood by Southern blot or PCR; a chromosomally abnormal T-cell clone.

A baseline workup for a SS patients should include a peripheral blood T-cell panel, CBC with manual differential and platelets, a skin biopsy with tissue frozen for immunohistochemistry and TCR gene rearrangement, chest x-ray, computed tomography (CT) scans of chest, abdomen, and pelvis, bone marrow biopsy with flow cytometry, and lymph node biopsy or fine needle aspiration. The lymph nodes of SS characteristically show a rather monotonous and diffuse infiltration with Sèzary cells and a varying degree of architectural effacement. CT scans of chest, abdomen and pelvis are used to evaluate adenopathy. However, positron emission tomography (PET) and PET/CT scans are emerging as a novel functional imaging technique that is more precise than conventional scintigraphy. Unlike CT scans, PET does not require lymphadenopathy, but does require sufficient numbers of tumor cells to be present with altered biochemical function to visualize these disease sites.

**SKIN DIRECTED PALLIATIVE CARE**

Skin diseases are particularly disabling because it affects their appearance and overall self esteem. Topical treatment in SS can be extremely helpful and includes supportive therapies that minimize skin irritation, provide lubrication and adequate hydration, and ameliorate inflammation. Skin exfoliation results in a violated protective barrier leaving affected individuals at risk for bacteremia. Our previous study showed that SS patients carry Staphylococcus aureus that contains superantigens driving T-cell proliferation. Colonization of the skin in SS is often accompanied by worsening erythroderma and with increased number of circulating Sèzary cells. Staphylococcus erythrogenic toxins also flare erythroderma of SS. The most common cause of death in CTCL is sepsis and is often related to the use of catheters placed through colonized skin. Common organisms are S. aureus, including methicillin resistant Staphylococcus, Enterobacteriaceae, and Pseudomonas aeruginosa.
We have found that continuous anti-staphylococcal antibiotic coverage and eradication of Staphylococcus colonization of the skin and nares is helpful in controlling erythroderma and in preventing fatal sepsis. Topical mupirocin ointment to nares as well as areas of open skin, such as fissures on hands and feet protects the skin barrier and reduces risk of infection and cellulitis. Patients are instructed to rinse with an acetic acid compound (one part acetic acid to four parts water) after bathing as low pH inhibits S. aureus growth on skin.

Patients with SS have depressed T-cell function predisposing them to opportunistic skin infections. In addition to S. aureus, dermatophyte infections are commonly found in keratoderma, i.e. the thick keratin layers of skin on the palms and soles of patients with SS. All patients with keratoderma should have scrapings tested by KOH examination for fungal elements, and preferably a fungal culture for dermatophytes. If tinea is present, appropriate topical antifungal therapy with a high potency gel to the whole area is recommended and should be continued long term. If dermatophyte infection is severe or involves a large percentage of the body surface area, oral anti-fungal therapy with oral terbinafine for several months is warranted.

Pruritus is the most bothersome symptom in SS and can cause great morbidity and disrupt the quality of life. Oatmeal baths and mild soap or Cetaphil is also soothing, and detergent soaps should be avoided. For skin dryness, we have found that lubrication with glycerin based moisturizers after bathing is of great benefit. Application of Sarna lotion with menthol is sometimes soothing for the pruritus. Although there is no cure for pruritus short of eradicating the disease, oral antihistamines given on a regular schedule can provide some relief. Non-sedating antihistamines should be prescribed for use during the day, while sedating antihistamines, such as hydroxyzine or diphenhydramine, are best used at bedtime. Oral sinequan, taken three times daily at doses of 25-50 mg and especially at bedtime, can be effective for pruritis in some patients. Gabapentin has been of some benefit for relief of itching as well. Starting dosage is 300 mg three times daily, and may be titrated to higher doses.

Mid-potency topical steroids, such as triamcinolone, kill T-cells and provide relief from pruritis if used regularly. We recommend SS patients to rinse off with 25% acetic acid after a bath or shower, apply mupirocin to areas of broken skin, then apply topical triamcinolone 0.1% ointment or cream to the body surfaces, avoiding axillae and groin. To increase the penetration, the skin can be covered with warm, wet towels for 15 to 20 minutes. Oral and systemic corticosteroids are also effective but their administration is often associated with severe flares when they are tapered or withdrawn. Thus, topical steroids directed to the skin lesions are more accepted and less likely to cause rebound flaring. High potency topical corticosteroids should be reserved for small areas and recalcitrant lesions. Attention to steroid induced adrenal insufficiency that can present as hypotension, hyperkalemia, and eosinophilia is required in SS patients using chronic steroids given systemically as well as topically.

**THERAPY OF SÉZARY SYNDROME.**

Although advanced SS is rarely cured, early diagnosis can improve the response rate; therefore, early recognition of SS is crucial. Patients with late stage CTCL and disease progression to blood or nodes have the least likelihood of a sustained clinical remission, and most tend to relapse within a few weeks to months of ending treatment. Thus, the treatment and symptom palliation needs to be ongoing and constant over a long period of time. Disease recurrence after systemic combination chemotherapy (ESHAP) indicated a poor outcome and patients become more refractory to further treatment over time.

**PHOTOPHERESIS AND BIOLOGICAL RESPONSE MODIFIER THERAPY**

Sézary patients have profound immunodeficiency and are atopic with excessive Th2 cytokine production, including IL-10 and IL-4. Thus, restoration of Th1 cytokines can improve their disease status and symptoms if instituted early in their course. This immunodeficiency leads to opportunistic infections. The first line of therapy in SS patients should be use of immunomodulatory therapy including photopheresis with or without biological response modifiers that include interferon, cytokines, or retinoids. Extracorporeal photopheresis (ECP), or photopheresis, combines leukapheresis with photochemotherapy directed to the circulating lymphocytes. Leukocytes are removed from the patient and they are exposed to first to psoralen (UVADEX) and then to ultraviolet A (UVA) radiation. The light causes the lymphocytes to undergo apoptosis and activates the patients’ dendritic cells which are then reinfused into the patient's blood stream. Photopheresis works best when CD8+ T-cells are present and may work by inducing further CD8+ T-cell responses against expanded T-
cell clones. Treatments are given two days in a row, usually every four weeks. This is an effective treatment for SS patients, although it is usually given in conjunction with other chemotherapeutic agents.

Unlike chemotherapy, photopheresis has been shown to prolong the survival of patients with SS, although this is still controversial. When used as a single therapy, photopheresis response rates are about 50% with about 15% of patients achieving complete responses. The best responses to photopheresis occur in when treatment is initiated early in the course of disease so that patients are immunocompetent and have not yet developed CD8 lymphocytopenia. When combined with biological response modifiers such as interferon alfa, GM-CSF or bexarotene, or total body surface electron beam, higher and prolonged response rates have been reported. Again, if a response to photopheresis is obtained, the procedure should be continued for another 6 months before an attempt to slowly taper the frequency is made.

Interferons are naturally occurring cellular glycoproteins that act as biologic response modifiers with antiviral, antitumor, and immunomodulating properties. Interferon-alpha (and interleukin 12) alters the T-cell phenotype from a Th-2 (interleukin [IL]-4- and IL-5-producing) cytokine profile towards a Th-1 (interferon-gamma- and IL-2-producing) profile. This is important because peripheral blood mononuclear cells from Sèzary patients have acquired a Th-2 cytokine phenotype producing IL-4, IL-5, and IL-10. The optimal dose of interferon alpha in CTCL has not been established and clinical responses are higher in untreated patients. Varying dosages and treatment schedules are used, but higher doses (over 3 million units per dose) are not well tolerated depending on patient's age. Interferon is associated with flu-like symptoms including fever, chills, myalgia, fatigue and depression. Taking interferon at night with pre-medications (acetaminophen or ibuprofen) is associated with improved tolerability. Myelosuppression, anemia, thyroid dysfunction, and hepatotoxicity are not uncommon and lab studies should be monitored at least monthly. Higher rates of remission are seen with interferon used for early stage CTCL patients. Stage IV patients had lower response rates (8% to 16%) when used as monotherapy. For this reason, at our institution, interferon is combined with other systemic treatments, such as retinoids and photopheresis for treatment of late stage CTCL and SS patients. Patience may develop antibodies to interferon over time which will reduce the efficacy.

Intravenous Ontak™ (denileukin diftitox) is a fusion toxin (DAB$_{389}$ IL-2) that has been approved for the treatment of refractory CTCL. Ontak™ contains the binding portion of IL-2 to target the IL-2 receptor on T-cells and introduce diphtheria toxin. Lymphoma cells, expressing the high affinity IL-2 receptor containing all three chains, are able to internalize Ontak™ resulting in cell death through inhibition of protein synthesis. It is possible to detect the presence of the IL2-receptors using fresh-frozen tissue stained for CD25 (the alpha chain) although the level of its expression needed for the therapy to be effective is not yet clear. Ontak™ has acute and chronic side effects. Infusion reactions commonly experienced include fever, chills, back pain and nausea, and rarely hives or anaphylaxis. Infusion reactions can be blocked by administration of antihistamines, acetaminophen, and low dose corticosteroids.

Depending on the trial, up to 27% of patients treated with Ontak™ may experience capillary or vascular leak syndrome (VLS). This is defined as hypoalbuminemia, hypotension, peripheral edema and weight gain. It generally occurs by day 10 of the first course of therapy and is less likely to reoccur. Most patients are asymptomatic, although some will develop pulmonary edema and require hospitalization. VLS can possibly be prevented or decreased if Ontak™ is followed immediately by an infusion of saline after drug administration. Ontak™ may damage the kidneys leading to loss of protein and hypoalbuminemia. Low albumin is also a contra-indication to use of Ontak™. Moderate improvement in the skin has been observed in Sèzary patients treated with Ontak™ and there was a 30% overall response rate in patients on the Phase III clinical trial comparing 9 to 18 mcg/kg/day administered every three weeks. Some patients have experienced flares of their erythroderma which were secondary to S. aureus, thus, skin cultures and bacterial prophylaxis may be desirable prior to initiating Ontak™. IL-2 administration also has been shown to exacerbate S. aureus colonization and induce erythroderma.

Retinoids are vitamin A analogues that have been used alone and in combination with other chemotherapeutic agents to treat SS. Tretinoin and etretinate have been commonly used retinoids in the past and have a response rate of about 50%. Isotretinoin is given at 1 mg/kg divided in two doses, and etretinate or its replacement, acitretin is given at 25 mg daily. Side effects, such as cheilitis and arthralgias at larger doses can limit its use, although favorable responses have been seen when combined with other agents. Bexarotene is
the first RXR selective retinoid which was approved in 1999 for the cutaneous manifestations of MF in both early and advanced patients. These studies showed an overall response rate of 45-55% in early versus late patients treated with the recommended dose of 300 mg/m²/day. In the advanced study, 44% of the patients with erythroderma and SS had partial responses to bexarotene as a single agent.

The optimal dose of 300 mg/m² is not tolerated in patients who have familial hypertriglyceridemia and high baseline fasting triglyceride levels. Elevated triglycerides produced by bexarotene can often be controlled using concomitant lipid-lowering agents. Fenofibrate (Tricor™) 160 mg is most frequently used because it targets triglycerides specifically. We have found that it may be combined with atorvastatin (Lipitor™) up to 80 mg as needed with the caveat that rhabdomyolysis is a potential possible adverse event. Fasting triglycerides should be maintained below 400 mg/dl and are more easily controlled if the patient is rendered euthyroid.

Bexarotene is known to suppress thyrotropin secretion, causing dose related, central hypothyroidism. In this setting, the TSH levels remain suppressed while the patient is on bexarotene and it is adequate to monitor the free T4 levels every two weeks initially until the dosage of bexarotene and levothyroxine is stable. Bexarotene as a monotherapy is effective in stabilizing or resolving the erythroderma of SS patients and is well tolerated with minimal symptoms and a favorable side-effect profile. Our previous work has shown that bexarotene in combination with photopheresis or with interferon can achieve response rates as high as 70-90%.

SINGLE AGENT CHEMOTHERAPY:
NUCLEOSIDE ANALOGUES

Pentostatin is a nucleoside analog that inhibits adenosine deaminase. Used alone or in combination with interferon alpha, partial responses have been seen in CTCL patients. In a phase II study involving pentostatin and high-dose interferon alpha, two patients with Sézary syndrome had a complete response (CR) and one has maintained remission for more than five years. Other trials have revealed a 70% overall response rate and a 25% CR when used alone. Durations were short, however, with 3.5 months the average for SS patients, with at least one SS patient achieving a long-lasting complete response of five years.

Fludarabine is a nucleoside analogue that resists deamination by adenosine deaminase and is phosphorylated to F-ara-AF-

Fludarabine is associated with significant and long-lasting bone marrow suppression and response rates are not durable. It only has a 19% partial response (PR) in CTCL. Gemzar is another nucleoside analogue, a pyrimidine with a lower toxicity profile that some of the agents mentioned above. Gemzar has been reported to induce a 70% partial response rate in late stage MF patients with minimal side effects. Gemzar is effective in decreasing tumor burden and is a useful agent for tumor stage disease. However, as with other single-agent chemotherapeutics, responses are not durable. In our Phase II clinical trial at MD Anderson, two patients with Sezary Syndrome in a study of 25 CTCL patients treated with gemcitabine developed the hemolytic uremic syndrome, which is stated to occur at a frequency of 0.6%.

COMBINATION CHEMOTHERAPY

Combined modality treatment was used as a frontline therapy at MD Anderson Cancer Center from 1987 until recently. This regimen consists of two treatment arms, one for early stage and another for late stage disease. The regimen for late-stage disease (Stage IIB – IVB) includes initiation with a combination of tretinoin and subcutaneous interferon for four months, followed by combined cyclophosphamide, methotrexate, etoposide and decadron (CMED) chemotherapy, then total body surface electron beam radiation. Electron beam irradiation is depth-limited and does not penetrate deeper tissues and organs. In early stage patients, chemotherapy is omitted, and both groups of patients receive maintenance treatment with topical nitrogen mustard and interferon alpha. One of three patients with SS had a long-lasting complete clinical remission on combined modality treatment, and 6 of 6 patients with Stage IVB disease had partial or complete responses with subsequent relapses within a year. The latter observation has motivated us to consider additional therapy with a matched donor allogeneic bone marrow transplant in patients who achieve complete responses and have an acceptable donor and risk profile. Stem cell transplantation from a matched related donor is not tolerated in patients with familial hypertriglyceridemia and high baseline fasting triglyceride levels.

Fludarabine is another nucleoside analogue which is phosphorylated to F-ara-AF-

Cyclophosphamide, vincristine, doxorubicin and prednisone
Diagnosis and Treatment of Sézary Syndrome

(CHOP) are commonly used to treat advanced CTCL. The combination is associated with bone marrow suppression which may be severe, although response rates are high. Other commonly used chemotherapy regimens include ESHAP, EPOCH, COP, COMP. Overall, no single-agent or multiagent regimen appears to produce significantly better responses than the others. Methotrexate at high doses remains one of the most active agents for the treatment of this disease and can be used as a single oral agent in SS. The combination of low dose oral chlorambucil with prednisone is a popular therapy developed at the Mayo clinic, and has been beneficial in ameliorating SS patients. Chemotherapy has the disadvantage of requiring catheters to administer and being myelosuppressive. Thus, patients with SS not uncommonly are infected and become septic while receiving chemotherapy.

EXPERIMENTAL TREATMENTS

In the setting of refractory Sézary Syndrome, patients should be offered the opportunity to enter clinical trials of new agents directed towards the malignant T-cell. These patients however have significant skin related morbidity including pruritus and S. aureus infections and they do poorly with catheters. Thus, trials should be designed that provide a reasonable amount of palliative therapy to give stable disease while the new agent is introduced. Use of flow cytometry allows the blood response to be monitored as well as the skin, which often fluctuates daily with respect to Erythema and scale. There are a number of exciting new agents that appear to be active in SS patient which are in current clinical trials. These include the histone deacetylase inhibitors (intravenously administered depsipeptide or oral suberoylanilide hydroxamic acid), monoclonal antibodies (HuMax targeting CD4+ T cells), and a small molecule inhibitor of purine nucleoside phosphorylase (Bcx 1777). Other agents as well as new experimental approaches are expected as a result of the explosion of knowledge in understanding the basis of this lymphoma.

CONCLUSION

Sézary syndrome (SS) is one of the cutaneous T-cell lymphomas with the poorest prognosis; the mean survival is less than two years. The classic triad of symptoms upon diagnosis are erythroderma, lymphadenopathy and pruritis. Early detection of this disease may help prolong survival. Recalcitrant erythroderma with or without pruritis should be investigated by means of a skin biopsy, peripheral blood T-cell panel and gene rearrangement analysis. A clonal proliferation is a sign of malignancy and will help distinguish between erythroderma and SS. If SS is diagnosed, a staging work up should be instituted promptly along with a treatment regimen. Single-agent chemotherapeutics are rarely effective at producing a complete response. Rather, combined modality regimens are most effective in producing remissions. Extracorporeal photopheresis has also been shown to prolong survival of SS patients. Skin is often colonized with Staphylococcus aureus bacteria and topical and oral antibiotics are a standard part of the treatment regimen for Sézary patients. Also helpful is application of a midpotency topical steroid under occlusion to relieve pruritis.

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References


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