

Long term Complete Response to Bexarotene, Photopheresis and Ampicillin

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Abstract

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She is certified in Internal Medicine and Dermatology. She has been a principal and co-principal investigator on numerous clinical trials studying the immunology of T-cell mediated disorders and skin cancers, as well as clinical drug development and translational research in T-cell lymphomas, melanoma, and various skin cancers. A prolific author, she has written manuscripts, book chapters, abstracts, and over 300 peer-reviewed journal articles. She is co-author on a recent book on Retinoids and Carotenoids in Dermatology.

INTRODUCTION

The most common variants of Cutaneous T-cell lymphoma (CTCL) are Mycosis fungoides (MF) and its erythrodermic, leukemic variant, Sézary Syndrome (SS).¹ In 1938, Albert Sézary originally identified very large atypical mononuclear cells ('cellules monstreuses')² in the blood of patients with generalized erythroderma. By convention, patients classified as having Sézary syndrome (SS) present de novo with exfoliative erythroderma defined as over > 80% body surface area and "significant" blood involvement, plus or minus lymphadenopathy. MF patients can also evolve into Sézary Syndrome. An absolute manual Sézary cell count proposed by Vonderheid for staging system of E-CTCL was based solely on Sézary cell counts: B0<1000 (1.0 K L-1); B1>1,000-4,999; B2 >5,000.³ Patients with Sézary

Syndrome are reported to have a poor median survival of 2-4 years.⁴ Our recent analysis found that overall median survival was 2.4 years for SS >10,000 SS cells, 5.4 years for SS with <10,000 SS cells, and 7.6 years for erythrodermic MF.⁵ The leading cause of death in SS patients is Staphylococcal sepsis and we have reported that SS patients have a 48% incidence of skin Staph aureus colonization that is associated with clinical flares.⁶ This case illustrates treatment of an erythrodermic patient with SS.

INITIAL PRESENTATION

1. PATIENT COURSE

A 63-year-old white female presented with an 8 year history of a pruritic erythematous rash on her inner thighs and knees that started while she was on a cruise ship. The rash improved transiently with topical steroids, but rebounded when they were stopped. Skin biopsy was inconclusive. She received UVA for several years with only minor and transient improvement. She developed exfoliative erythroderma with severe pruritus and keratoderma. In 1998, repeat skin biopsy showed MF and she was referred to our CTCL clinic.

PAST TREATMENTS

1. Topical steroids - improved, but relapsed and flared with discontinuation.
2. Ultraviolet A therapy – transient improvement, relapsed, and progressed.
3. Prednisone (oral) - 09/98; tapering dose rebounded.

HISTORY AND PHYSICAL

At initial presentation, she was fatigued and with visible shaking chills. Generalized exfoliative erythroderma was present. (Figure 1A) There were fissures on the shins and feet

with keratoderma present. (Figure 2A,C) Skin score was 350 out of 400. (Figure 3)

CLINICAL LABORATORY FINDINGS

Complete blood count (CBC) with differential may help to diagnose early SS. On differential, atypical cells may mask as monocytes and lymphocytosis, and/or eosinophilia can be present. Large cells with lobular, convoluted “cerebriform” nuclei were present on her peripheral smear (Figure 4). A CD3+CD7- clone was present at 45% of her circulating lymphocytes. Lesional skin biopsy showed an atypical T-cell dermal lymphoid infiltrate with epidermotropism consistent with mycosis fungoides. Nasal and skin cultures grew methicillin resistant *Staphylococcus aureus* (MRSA).

Figure 1

Figure 1. (A) Pre ECP, (B) Pre Bexarotene, (C) Post Bexarotene

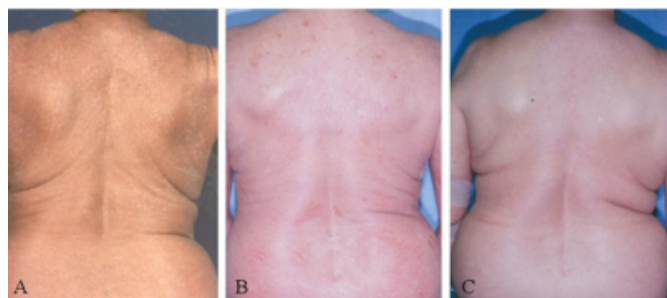


Figure 2

Figure 2. (A) (C) Pre- Bexarotene, (B) (D) Post- Bexarotene



Figure 3

Figure 3. Skin score plotted for 67 visits over a period of 10 years from 1998 to 2008

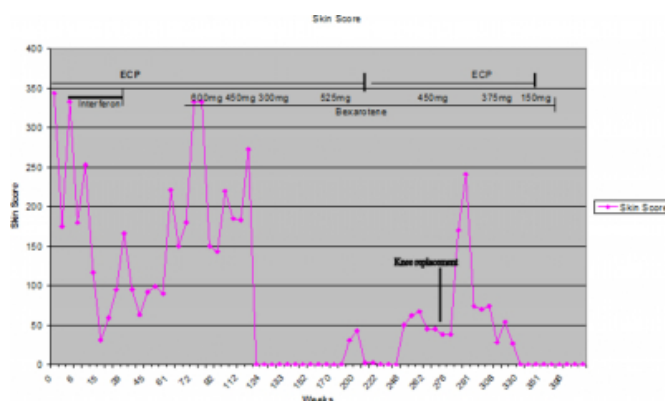
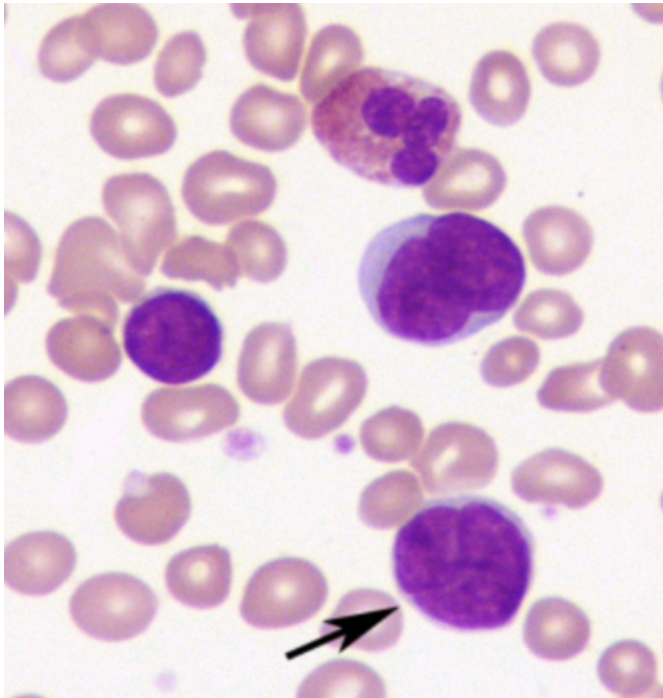


Figure 4

Figure 4. Sèzary cells which are large activated T-cell lymphocytes have a lobular, convoluted “cerebriform” nucleus and are seen on peripheral smear



CONSIDERATION FOR DERMATOLOGIST/ONCOLOGIST FROM REFERRING PHYSICIAN

Early diagnosis of SS in an elderly person with pruritis with or without low grade erythroderma is very often missed by primary care physicians. Patients are written off as having senile xerosis or eczema. It is common for the skin biopsy to show a dermal atypical perivascular lymphoid infiltrate without the epidermotropism required for diagnosis of MF. Once a diagnosis of SS is made, if the patient is referred to an oncologist, chemotherapy rather than immunomodulatory therapy is most often chosen and use of indwelling catheters for chemotherapy may initiate Staph sepsis and death. Skin care, including eradication of Staph aureus and use of topical rather than oral steroids, is most essential for these patients to improve and chemotherapy may cause disease progression.

DIAGNOSIS AND STAGE

Sézary syndrome evolving from erythrodermic Mycosis Fungoides based on biopsy showing MF, generalized erythroderma, and aberrant blood clone, negative node and bone marrow Stage III (T3,NO,MO,B2).

TREATMENT OPTIONS FOR SEZARY

SYNDROME:

1. PALLIATIVE SKIN CARE, ANTI-STAPH REGIMEN

Immunomodulatory therapy (Interferon, bexarotene and ECP) or total skin electron beam followed by allogeneic non-ablative transplant

Immunosuppressive therapy – Denileukin diftitox, vorinostat or Histone Deacetylase inhibitors, Experimental – Forodesine or Humax CD4, Campath H1, prednisone, methotrexate, pentostatin, gemcitabine, doxil

MANAGEMENT

Rationale for treatment selection: This patient’s course and disease was characterized by waxing and waning of her erythroderma over the course of several years with flares occurring whenever her skin was colonized with Staph aureus or enterococcus. She did not have bulky nodal disease or high white count or bone marrow involvement so we tried to get her skin uncolonized and start biologic response modifier therapy which is slow but can induce complete remissions in patient patients.

Multi-disciplinary Team Considerations: We could have recommended total skin electron beam radiation followed by non-ablative allogeneic transplant in a younger patient with a matched related donor. Because of her age and stage, we elected front-line biologic immunomodulatory therapy. Her pre-existing thyroid disease which was labile and symptomatic requiring very high medication doses made us seek the help of an endocrinology consultant.

CLINICAL COURSE AND EVIDENCE AND FOLLOW-UP:

This patient, like many erythrodermic SS patients, experienced multiple, dramatic partial responses to intense courses of intravenous Vancomycin, hibiclens wash with 0.025% acetic acid rinses, and triamcinolone 0.1% wet wraps daily in the hospital which relieved her symptoms for several months at a time.

Her treatment course is shown in Figure 1. Alpha interferon at 3 million three times per week gave partial response in skin score to <50 during week 4-33. (Figure 3). When interferon was discontinued at week 33 for severe depression, her skin score returned to baseline. Extracorporeal photopheresis was started at two days per month in Oct 1998 (week 0, figure 1A) and continued through (week 333) December 2004 for a total of 95 courses. In March 2000 (week 69, figure 1B), bexarotene was added

at a dose of 600 mg/day (8 capsules) with oral synthroid and fenofibrate (Figure 1B, Figure 2A, C). She took herself off medication and her skin rapidly worsened.

Oral bexarotene was reintroduced at 450 mg/day with (week 96) higher thyroid replacement dose of 250 mcg/day (Figure 3). In January 2001, (week 120) her skin was normal, no pruritus was present, and there was a documented reduction in Sézary cells from 65% to 0% by flow cytometry. When her bexarotene dose was slowly tapered to 300 mg/day her skin relapsed in (week 146) June 2002. (Figure 3) Bexarotene was increased to 525 mg and she again was in complete remission for several months.

In November 2003 (week 271), a cadaver knee graft was placed and became infected with enterococcus. This was accompanied by progression back to generalized erythroderma. She was hospitalized for one month for IV vancomycin and ampicillin. She was then placed on chronic amoxicillin 1 gm/daily. In December 2004 (week 333) her skin became completely normal again. The bexarotene was tapered very slowly from 6 capsules to zero by March 2006 (week 396). (Figure 1C, Figure 2B, D and Figure 3) She remains in complete remission on amoxicillin as of October 2009.

TREATMENT GUIDELINES

SKIN DIRECTED CARE:

Pruritus is the most bothersome symptom in SS, causing significant morbidity. Skin is often colonized with *Staphylococcus aureus* bacteria and topical and oral antibiotics are a standard part of the treatment regimen for Sézary patients. We now recommend that patients bathe with hibiclens, anti-bacterial soap, dove, cetaphil, or Oatmeal baths. Detergent soaps should be avoided. Dry skin causes worsening and promotes staph carriage. Therefore, after bathing, rinse the skin with 1 parts white vinegar to 4 parts water and apply moisturizer. Lachydrin 5 has low pH and that also reduces *Staph aureus*. Cetaphil (glycerin based) or Cerave (lipid based) are also excellent emollients, as are Aquaphor or Vaseline for very scaly patients. After moisturizing we recommend application of topical triamcinolone cream to red areas, and hydrocortisone in eucerin for groin, axilla, and face. To increase the penetration, the skin can be covered with warm, wet towels for 15 to 20 minutes.

Pruritus: Non-sedating antihistamines (Zyrtec, hydroxyzine) can be prescribed for use during the day, while sedating

(diphenhydramine) are best used at bedtime. Doxepin 25 mg po TID with 50mg at bedtime or gabapentin 300 mg three times daily has been of some benefit for relief of itching as well. Doxepin interacts with linezolid and other antibiotics.

SAFETY CONSIDERATIONS

Patients with SS have depressed T-cell function predisposing them to opportunistic skin infections and many do not mount a fever when they are septic, rather they become hypothermic. Colonization with *Staphylococcus aureus* precludes the use of indwelling catheters due to frequent line sepsis or even death. Topical and oral antibiotics should be a standard part of the treatment regimen for Sézary patients and based on culture results.

TEACHING POINTS

EXTRACORPOREAL PHOTOPHERESIS (ECP)

Extracorporeal photopheresis (ECP), or photopheresis, combines leukapheresis with photochemotherapy directed to the circulating lymphocytes. 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. When used as a single therapy, photopheresis response rates are about 50% with about 15% of patients achieving complete responses. ⁸

INTERFERON-ALPHA

Interferon-alpha 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. ⁹ The optimal dose of interferon alpha in CTCL has not been established and varying dosages and treatment schedules are used, but higher doses (over 3 million units per dose) are not well tolerated in older patients. Interferon is associated with flu-like symptoms including, fever, chills, myalgia, fatigue and depression.

RETINOIDS (BEXAROTENE)

Bexarotene is the first RXR selective retinoid 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.

¹⁰

CONCLUSIONS

1. Palliative therapy in SS patients includes topical (not oral) steroids plus removal of Staph aureus colonization.
2. Extracorporeal photopheresis plus biological response modifiers are able to induce complete remissions and prolong survival of SS patients. The course of SS patients waxes and wanes and patience is needed to achieve complete responses in these difficult, symptomatic patients.

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