Long term Complete Response to Denileukin Diftitox and Bexarotene

M Duvic, R Talpur

Citation

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Abstract

Madeleine Duvic, MD, is Professor of Internal Medicine and Dermatology, and Deputy Chairman of the Department of Dermatology at The University of Texas, M. D. Anderson Cancer Center in Houston, Texas. She is a founding member of the United States Cutaneous Lymphoma Consortium (USCLC), a Board member of the International Society for Cutaneous Lymphoma, and also serves as Director of The Cutaneous Lymphoma Clinic at MD Anderson Cancer Center. Dr. Duvic has also served on the Board of Directors of the American Academy of Dermatology (AAD).

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 of a recent book on Retinoids and Carotenoids in Dermatology.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) arise from malignant T-cell clones that home to the skin producing pleomorphic cutaneous manifestations. The most common variants are mycosis fungoides (MF) and its leukemic form, the Sézary syndrome (SS). 1 The overall age-adjusted incidence of CTCLs from 1973 to 2002 was 6.4 cases per million and Mycosis Fungoides accounted for 72% of these CTCL, whereas the Sézary Syndrome accounted for 2.5%. The incidence was roughly 50% greater in African American than in Caucasian people. 2

Mycosis fungoides and Sézary syndrome are seldom cured by therapy and therefore the goals of the treatment are to control the disease and improve the quality of life. The purpose of this case report is to show the value of sequential combination therapy for improving overall response in advanced stage patient.

INITIAL PRESENTATION PATIENT COURSE & PAST TREATMENTS

A 72-year-old white female with a diagnosis of Mycosis Fungoides, Stage IIB presented to MD Anderson for treatment options. Fifteen years ago she had noted a sun induced rash on her arms, diagnosed as systemic lupus erythematosus and clearing with oral and topical steroids. In 2000, nodules appeared but resolved with intralesional steroids. A year later, she developed a new nodule and biopsy showed cutaneous malignant lymphoma, CD3+ T cell phenotype. It resolved after 15 radiation treatments. In May 2003, she developed multiple new pruritic papules and patches classified as a peripheral T cell malignant lymphoma with phenotype CD3+CD4-CD8-CD30-CD56-. Her lesions progressed on topical steroids so she began oral isotretinoin 70 mg once daily and interferon 3million units x 3 per week for 7 months. There was initial improvement followed by progression.

HISTORY

The past history included hypercholesterolemia, hypothyroidism, and mild carotid stenosis. She was allergic to penicillin and sulfa drugs. She lived in Los Alamos, New Mexico and gave a history of possible exposure to radiation.

PHYSICAL EXAM

At presentation she had pleomorphic, oval to round pink, violaceous, red and brown patches and plaques and tumors on her lower abdomen (Figure 1A, 1B) and buttocks. Total involvement was 6.75% (plaque 5.75%, tumor 1%). She had alopecia with impetigo of the scalp which grew staph aureus.

No lymphadenopathy was present.

Figure 1

Figure 1. (A) Plaques on anterior trunk (B) lesion # 1.

(A)



Figure 2



CLINICAL LABORATORY FINDINGS

Her previous workup had included negative ANA, negative ESR, and negative rheumatoid factor in 05/99. In 2002 she had a CT of the chest, abdomen and pelvis, PET scan and bone marrow biopsy that showed no evidence of disease. Hepatitis C virus antibody was positive but RNA was negative by polymerase chain reaction (PCR).

PATHOLOGY

The lesional skin biopsy showed pronounced T-cell epidermotropism as well as Pautrier's microabscesses, interpreted as Mycosis fungoides. Rare atypical epidermal T- cells were strongly positive CD25 although only 10% of the cells stained. (Figure 2) A T-cell gamma receptor gene rearrangement was detected by PCR. A CD25 staining in a pre-treatment skin biopsy was only CD25 positive in <1% of lymphocytes.

Figure 3

Figure2. Immunochemical staining for CD25 in lesional MF biopsy specimens. CD25+ lymphocytes are present (a) at the dermal/epidermal interface (original magnification 100X) (b) in a Pautrier's microabscess in the epidermis (original magnificat



DIAGNOSIS AND STAGE

Mycosis Fungoides stage IIB (T3N0M0) with plaque and tumor involvement.

Consideration for Dermatologist/Oncologist from Referring Physician. The patient was initially misclassified as having a peripheral T-cell lymphoma rather than MF which has a more aggressive course, needs more aggressive therapy and has a worse prognosis. If the patient had not responded to denileukin diftitoxin or single agent chemotherapy, then combined chemotherapy might be considered. Treatment options for IIB Mycosis Fungoides: This patient has failed biological response modifiers – RAR retinoids and interferon. Oral bexarotene plus a skin directed therapy such as nitrogen mustard or local radiation could be tried initially. However, her lesions were becoming tumors rapidly, hence a tumor debulking agent such as denileukin diftitoxin, even though she had limited expression of CD25+ cells, selected initially. Monochemotherapy with either gemcitabine or doxil were other good options for this patient.

MANAGEMENT

Rationale for treatment selection: denileukin dititox has shown good efficacy in debulking tumors with the potential of complete responses in 10% of the patients. It is less immunosuppressive than chemotherapy, which is an important consideration for CTCL.

MULTIDISCIPLINARY TEAM CONSIDERATIONS

More immunosuppressive chemotherapy, either gemcitabine or liposomil doxil, is effective for tumor stage MF. This patient was chemotherapy naive so we elected front-line biologic immunomodulatory therapy. Initially the patient had an incorrect diagnosis of peripheral T-cell lymphoma but clinically her lesions fit better with Mycosis fungoides so she was referred from oncology to the dermatology CTCL clinic for care. MF from a node or tumor can easily be misdiagnosed as peripheral T-cell lymphoma because there is no possibility of seeing epidermotrophism.

CLINICAL EVIDENCE

In May, 2004 she was enrolled on an experimental Denileukin dititox (Dd) protocol for patients irrespective of the CD25 status. The scalp grew staphylococcus, treated with clindamycin. Denileukin diftitox was infused at a dose of 18mcg/kg = 1276 mg x 5 days every 21 days. On day 4 she developed a maculopapular rash on her extremities. A biopsy was consistent with a lichenoid drug reaction. By day 9, her rash spread all over the body and blisters formed. Clobetasol propionate and triamcinolone creams were applied to the eruption. Tetracycline was substituted for clindamycin but she stopped after three days for nausea and vomiting. Yeast was present in the throat and treated with mycelex.

After course one of Dd there was significant improvement in her skin with flattening of all of her tumors. Her lichenoid rash remained on her arms and thighs. A second course of Dd was given at 9mcg/kg and she again had a generalized lichenoid drug eruption at day 4 (Figure 3A) and was more severe than the initial one. The MF improved by 50% to only 3.5% patches (Figure 3B) and resolution of all tumors and plaques.

Figure 4

Figure 3. Post denileukin diftitox 2 cycles (A) Rash after treatment with Dd C2 D21 (B) Lesion #1

(A)



(B)



Low dose bexarotene 225 mg was started with concommitant fenofibrate 145 mg and levothyroxine 75

mcg. After 3 weeks, her bexarotene dose was increased to 300 mg and levothroxine to 100 mcg. At 8 weeks, the dose of bexarotene was raised to 375 mg. For the 5 % remaining patch involvement, she was asked to apply topical mustargen (NM) in aquaphor. By week 32, the involvement of her MF was reduced to 0.5%. Bexarotene was tapered by one pill. By week 56, on 300 mg bexarotene, her MF lesions and alopecia had completely resolved.

Over the next year she continued to taper the bexarotene down to 225 mg and she was weaned off the topical NM. The duration of her complete response was 64 weeks. At week 120, she developed new pink patches involving 2% of her body. Bexarotene was further tapered alternating 150mg with 225mg every other day. By week 152 in August 2007, she reduced bexarotene to 150 mg and has continued on this dose through the present with only 1% patch disease.

TREATMENT GUIDELINES

Advanced stage patients often require sequential multiple treatment modalities including chemotherapy and radiation in order to obtain and maintain remissions. The most severe adverse effect of Dd is capillary leak syndrome (hypotension, edema and hypoalbumenia) which occurs in 20-30% of patients and can be prevented to some extent by hydration after the Dd infusion and administration of low dose systemic steroids to block infusion reactions. Whether Dd has better efficacy if the patient has CD25 staining greater than 20%. In our patient initial biopsy was 10% and later on repeat biopsy prior initiation of Dd was 1%.

SAFETY CONSIDERATIONS

When administering Dd, the patient should be watched closely for the signs of capillary leak syndrome which is present by day 10 if it is going to occur. Patients can monitor daily weight and ankle swelling.

TEACHING POINTS

1. Denileukin diftitox (Ontak[®]) binds to the high and intermediate affinity interleukin 2 receptors (IL-2R) on Tcells. Binding to a high affinity receptor is followed by internalization and cell death through inhibition of ADP ribosylation of elongation factor 2. ₃ The high affinity IL-2R is a complex consisting of two obligate subunits: IL-2R beta (CD122, p75) and gamma (CD132, p64); and a variably expressed IL-2R alpha subunit (CD25, p55). Although Ontak[®] binds to all three forms of the IL-2R, only cells with the intermediate or high affinity receptors will internalize the fusion protein. ₃ A phase II trial comparing two doses of denileukin diftitox showed clinical efficacy in the treatment of persistent or recurrent CTCL when > 20% of cells stained positive for the alpha chain (CD25) of the high-affinity IL-2 receptor. ₄ However, a paraffin assay developed at our institution was used to find that patients with high expression of CD25 had a 70% response rate compared to a 20% response rate in low expression patients. ₅

It should be noted that this patient had low expression of CD25 yet had an excellent response to Dd.

2. Bexarotene (Targretin; Ligand Pharmaceuticals) is a retinoid X receptor (RXR) selective retinoid that has demonstrated clinical efficacy in patients with early- and advanced-stage CTCL. 6 Bexarotene binds to and activates nuclear RXR receptors. The RXRs are unique in their ability to form heterodimers with all the other classes of nuclear receptors including retinoic acid receptors, vitamin D receptors, thyroid receptors, and peroxisome proliferator activator receptors. The major adverse effects are the hypertriglyceridemia, and hypothyroidism. The triglyceride lowering agent fenofibrate at 145mg daily should be started before a patient takes bexarotene and atovastatin can be added at 20-40 mg if there is high cholesterol. Fenofibrate and atorvastatin together should be used with caution since there is a small risk of rhabdomyalysis. Muscle symptoms and creatinine phosphokinase levels should be monitored. Thyroid hormone replacement is needed for all patients on bexarotene to keep the T4 in the normal range, usually 25 mcg per 75 mg or one tablet of bexarotene. TSH levels remain suppressed while patients on bexarotene.

CONCLUSION

Denileukin diftitox was successfully used as a tumor debulking agent followed by long-term maintenance with a combination of systemic oral bexarotene and skin-directed steroids and nitrogen mustard for six years. This patient had a hypersensitivity drug reaction to Dd which may have helped to clear her disease.

References

 Kim YH, Hoope RT. Mycosis fungoides and Sezary syndrome. Semin Oncol 1999;26:276-289.
VD Criscione and MA Weinstock, Incidence of cutaneous T-cell lymphoma in the United States, 1973–2002, Arch Dermatol 2007;143:854–859.
Waters CA, Schimke PA, Snider CE, et al. Interleukin-2 receptor-targeted cytotoxicity: Receptor binding requirements for entry of a diphtheria toxin-related interleukin-2 fusion protein into cells. Eur J Immunol 1990; 20(4):785-791.
Duvic M, Cather J. Immunotoxin DAB 389 Interleukin-2

4. Duvic M, Cather J. Immunotoxin DAB 389 Interleukin-2 (ONTAK®) in the management of cutaneous T-cell lymphoma. Curr Prac Med 1999; 2:8, 167-170. 5. Talpur R, Jones D, Alencar A, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. J Invest Deramtol, in press.

6. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol. 2001;19: 2456-2471.

7. Andres Negro-Vilar, Zofia Dziewanowska, Eric Groves, Elyane Lombardy, and Victor Stevens. Phase III Study of Denileukin Diftitox (ONTAK®) To Evaluate Efficacy and Safety in CD25+ and CD25- Cutaneous T-Cell Lymphoma (CTCL) Patients. Blood (ASH Annual Meeting Abstracts), Nov 2006; 108: 696

Author Information

Madeleine Duvic, MD

Division of Internal Medicine, Department of Dermatology, The University of Texas M.D. Anderson Cancer Center

Rakhshandra Talpur, MD

Division of Internal Medicine, Department of Dermatology, The University of Texas M.D. Anderson Cancer Center