Advanced Stage CTCL, PTCL with Cutaneous Involvement

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Citation

J Messenger, P Porcu. *Advanced Stage CTCL, PTCL with Cutaneous Involvement*. The Internet Journal of Dermatology. 2008 Volume 7 Number 3.

Abstract

Dr. Porcu obtained his medical degree in 1987 and Board certification in Medical Oncology in 1991 from the University of Torino, Italy. He then held a post-doctoral laboratory position at Temple University from 1990 to 1992 and was a research associate at Thomas Jefferson University from 1992 to 1993, both in Philadelphia, U.S. He completed a residency in Internal Medicine in 1996 and a Fellowship in Hematology/Oncology in 1999 at Indiana University, Indianapolis, IN. He is currently an Associate Professor of Internal Medicine at The Ohio State University (OSU) and a member of the Viral Oncology Group of the OSU Comprehensive Cancer Center (OSUCCC), where he conducts clinical and translational research in lymphoma. He is a faculty member inductee of the Alpha Omega Alpha.

Dr. Porcu's work has been published in Blood, Journal of Clinical Oncology, Clinical Cancer Research, Cancer Research, PNAS, Oncogene, and Molecular and Cellular Biology. Dr. Porcu was on the editorial board of the journal Leukemia from 2002 to 2005 and is a member of the Scientific Advisory Board of the Cutaneous Lymphoma Foundation (CLF). Since 2000 he has been a member of the NCCN committee for NHL practice guidelines. Currently his research focuses on the biology and experimental therapy of T-cell lymphomas and cutaneous lymphoproliferative disorders.

Dr. Porcu also works extensively in the field of lymphoma education and mentoring. He teaches numerous graduate and post-doctoral classes in the College of Medicine on the biology, diagnosis, and treatment of lymphoma and was recently selected as the Cancer Signature Program liaison of the OSUCCC for the OSU Research Education Council Committee. Dr. Porcu is very active in patient education forums, on behalf of patient advocacy organizations, such as the Cutaneous Lymphoma Foundation, CancerCare, and the Leukemia and Lymphoma Society.

INTRODUCTION

T-cell lymphomas (TCL) are a relatively rare form of non-Hodgkin lymphoma (NHL), representing approximately 10-15% of all NHL cases. TCL have a predilection for the skin and are therefore of great clinical interest to dermatologists and hematologists alike. Cutaneous T-cell lymphomas (CTCL) define a heterogeneous group of malignancies encompassing many different clinical and pathological presentations. Mycosis fungoides (MF) is the most common type of CTCL. While MF follows an indolent clinical course, other more aggressive forms of CTCL present a challenge to the clinician from both a diagnostic and treatment standpoint. It is not uncommon that MF and other types of CTCL may coexist in the same patient. Recent advances in drug development have increased the effectiveness of CTCL treatment.

INITIAL PRESENTATION

A 65-year-old Caucasian female presented to an outside oncologist with a progressively enlarging marble-sized lesion on her left posterior thigh without other cutaneous findings. A biopsy containing more than 90% tumor cells revealed a CD3+ CD4+ CD30- small to medium size T-cell lymphoma. Upon further immunophenotypic characterization it was found that CD10, CD20dim, and terminal deoxynucleotidyl transferase (TdT) were also expressed on tumor cells. The tumor showed monoclonal rearrangement of both the T cell receptor beta and immunoglobulin heavy chain (IgH) loci. Expert pathological review confirmed these findings. The expression of both CD10 and TdT, as well as the dual rearrangement, suggested a diagnosis or T-lymphoblastic lymphoma (T-LBL). However, the patient had no systemic symptoms, no findings of extracutaneous involvement and normal laboratory values. She was offered systemic chemotherapy for a presumptive diagnosis of limited stage T-LBL or peripheral T-cell lymphoma (PTCL) but she declined and elected to

receive radiation therapy to her thigh, which resulted in full resolution of her lesion.

After two years without progression, multiple new lesions appeared in the same location. The small, nodular lesions were again asymptomatic. Again a punch biopsy showed that the tumor cells were CD3+, CD4+, CD30- with aberrant CD20 and CD10 expression. This time, however, they failed to express TdT. TCR beta and IgH gene rearrangements were not analyzed. The diagnostic conclusion was peripheral T-cell lymphoma (PTCL) with aberrant CD20 expression. CT scans, PET scan and bone marrow biopsy showed no involvement outside of the skin. The patient once again declined systemic chemotherapy and received instead four weekly doses of rituximab, based on the perceived need for systemic therapy on the part of the oncologist and the expression of CD20 in the tumor cells. No response was observed and the patient was retreated with radiation therapy, leading to a second complete response. A few months later she developed a recurrence in the same location. At that point she was referred to the Ohio State University (OSU).

At presentation to OSU the patient complained of significant tenderness over multiple cutaneous nodular lesions, fatigue and night sweats, but her physical exam was otherwise unremarkable. Laboratory studies showed WBC of 3.4 with a normal differential, hemoglobin 14.1, platelets 235, and electrolytes, serum creatinine, transaminases and LDH in the normal range. A punch biopsy demonstrated a highly pleomorphic infiltrate effacing the dermal architecture and extending heavily in the subcutaneous fat. Tumor cells stained positively for CD3, CD10, and CD20 but this time they were CD8+ rather than CD4+. Granzyme B, TIA-1 and CD30 were negative. Flow cytometry showed no immunophenotypic evidence of an abnormal population of lymphocytes in the peripheral blood. TCR beta analysis of lesional skin showed a single monoclonal band and IgH showed a biclonal rearrangement. The patient received six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with complete resolution of the nodules. However a few weeks after completing therapy the nodules recurred and she was started on denileukin diftitox (DD, Ontak), 18 micrograms/kg IV on days 1-5. The clinical response was rapid and impressive. The lesions once nodular, erythematous and tender began to flatten with diminished surrounding redness. The patient received a total of 4 cycles of therapy, every 21 days, and tolerated the treatment well. She developed a hypersensitivity reaction and mild vascular leak syndrome (VLS) after her first cycle; her dose was reduced to 9 micrograms/kg for the remaining cycles. A subsequent follow-up three months after completion of therapy showed complete resolution of the lesions.

The patient was without any signs of progressive disease for 2.5 years, then presented with multiple flat, scaly patches of rash involving less than 10% of the body surface area (BSA). The patient denied pruritus, night sweats, or weight loss. A biopsy showed an epidermotropic CD4+ CD7- small cerebriform T-cell infiltrate, morphologically consistent with Mycosis Fungoides. CD8, CD10, and CD20 stains were negative. Molecular studies on the skin showed monoclonal and oligoclonal rearrangements of the TCR beta and IgH, respectively. She started topical corticosteroids. Within 2 months there was a significant progression of the rash to an estimated 30-40% BSA, with both plaque and patch stage lesions. No adenopathy was found on exam. Flow cytometry of peripheral blood revealed that T-cells represented 61% of the lymphocytes with a normal CD4:CD8 ratio but loss of CD26 expression on 43% of the T-cells. TCR beta analysis on the peripheral blood showed a monoclonal band. LDH was normal. The patient was started on PUVA.

After three months of PUVA therapy the patient had experienced only a very modest response and new plaque stage lesions began to develop. Oral bexarotene (225 mg twice daily) was started. The combination of PUVA and bexarotene resulted in a partial response, but within 3 months tumor stage lesions began to develop on the hips, axillae and lower extremities. At this point denileukin diftitox (DD) was again started at the18 micrograms/kg daily dose for 5 days every 21 days, while continuing bexarotene. Treatment was well tolerated but response was transient, even after increasing the frequency of DD administration to every 14 days. The patient developed numerous large (4-5 cm) tumor lesions. Restaging CT scans showed no evidence of visceral disease. The patient declined a repeat bone marrow biopsy. Interferon alfa-2b, 10-15 MIU subcutaneously thrice weekly was started and electron beam radiation was used to treat large refractory tumors. A bone marrow transplant consultation has been obtained. Therapy is ongoing.

CONSIDERATIONS FOR REFERRING DERMATOLOGIST/MEDICAL ONCOLOGIST

At the patient first visit, the initial biopsy suggested T-LBL, but the clinical picture and subsequent studies refuted this

diagnosis. Highly intensive combination chemotherapy was appropriately not given. The oncologist eventually determined the lesions to be limited stage PTCL and treated with involved field radiation. When the patient relapsed, two years later, it was concluded that systemic therapy was necessary but the patient declined aggressive lymphoma chemotherapy (CHOP). Therefore, the oncologist selected rituximab due to the aberrant expression of CD20 on tumor cells. It should be noted that the antibody used to detect CD20 expression by immunohistochemistry (clone L26) binds to the intracellular domain of the trans-membrane CD20 protein and that, although surface expression of CD20 generally correlates with L26 positivity, this assumption may not always be correct. The cutaneous lesions did not respond to rituximab and were again treated with radiotherapy leading to a second complete remission. When the patient was referred to the OSUCCC it was concluded that the patient's clinical and pathological picture was most consistent with a skin-limited PTCL. The presence of systemic symptoms was thought to reflect a more aggressive clinical course, compared to the initial presentation.

DIAGNOSIS

The treatment options at the time of referral to the OSUCCC were targeted to a lymphoma that was classified as a skin-limited CD8+ PTCL with aberrant CD20 expression and monoclonal IgH rearrangement. They included cytotoxic chemotherapy such as CHOP as well as non-chemotherapy options, such as retinoids such as bexarotene , phototherapy, interferon alpha, and denileukin diftitox (DD). CHOP was selected, but as is often the case in PTCL, it resulted in a very brief response. Denileukin diftitox, on the other hand, produced a very durable complete response (2.5 years). When the patient progressed the third time she did so with a different type of T-cell lymphoma: mycosis fungoides (MF).

STAGING OF CANCER

The patient was initially diagnosed with a stage I extranodal (skin) CD8+ peripheral T-cell lymphoma (PTCL). Multiple CT and PET scans failed to detect extracutaneous involvement with PTCL. When the patient developed MF, she presented with stage IA (T1N0M0), although she progressed to stage IIB (T3N0M0) relatively rapidly (less than 12 months). This accelerated tempo of progression is unusual in de-novo MF.

MANAGEMENT ISSUES

CHOP was the first treatment recommended by the referring oncologist. This decision was based on literature supporting the need for systemic combination chemotherapy for PTCL, even in early stage. However, due to patient refusal the oncologists chose radiotherapy, as the second tier treatment modality. This was effective but only for two years, reinforcing the oncologist's conviction, based on literature data, that systemic therapy is needed in PTCL. The patient again declined chemotherapy, though, forcing the oncologist to choose an alternative systemic therapy with a favorable toxicity profile. Despite the expression of CD20 on tumor cells (later confirmed at relapse) the choice of rituximab for this T-cell malignancy was unconventional and not evidence based.

When CHOP failed to produce a long-term resolution the patient received denileukin diftitox (DD), an FDA-approved CTCL treatment since1999 [1]. DD is an immunotoxin conjugate consisting of human interleukin-2 (IL-2) linked to the catalytic domain of the diphtheria toxin. DD selectively targets cells that express the high affinity IL-2 receptor (CD25). The clinical response to DD in this patient was remarkable. Following the first cycle the lesions began to flatten with a diminution of erythema before eventually completely resolving. As treatment continued the patient's energy level increased and the pain was no longer present, greatly improving the patient's quality of life. Microscopically, there was a vast reduction in the dermal infiltrate, and molecular studies revealed a polyclonal TCR population had emerged. Following treatment with DD the patient was essentially disease free for 2.5 years. The patient did experience some of the common side effects of DD, which include a hypersensitivity reaction and vascular leak syndrome. Additional side effects associated with DD include flu-like symptoms, hypoalbuminemia, transaminitis, renal insufficiency and edema, which can be prevented or diminished by premedication with corticosteroids.

CONCLUSION

This case was challenging from the diagnostic and the medical decision making standpoints due to the uniqueness of the phenotype exhibited by the T-cell lymphoma, its composite histology, the multiple relapses after therapy, and the relatively rapid transition from patch/plaque stage MF to aggressive tumor stage disease.

Initially, the aberrant expression of CD20, usually a cell marker restricted to mature B-cells, and the presence of a clonally-rearranged IgH significantly confounded the diagnosis and the treatment planning. However, the immunophenotypical studies showing expression of a wide

range of T-cell markers (CD2, CD3, CD5, CD4/CD8) combined with molecular studies showing TCR clonal rearrangement, and the clinical presentation and evolution support a diagnosis of TCL. CD20+ PTCL has been reported in the literature [2-5], but its significance in terms of prognosis and response to CD20-targeted therapy is unknown. In regard to the expression of CD10, there is evidence that CD10 may be expressed in a subset of PTCL (angioimmunoblastic) and is associated with apoptosis; therefore it does not necessarily reflect an immature T-cell population. The referring physician was appropriately suspicious of the diagnosis of T-LBL due to the clinical picture and therefore wisely delayed treatment until the diagnosis was certain. Once the malignancy was accepted as a PTCL the aberrant expression of CD-20 had to be considered.

While some hypothesize that CD20 expression in a TCL stems from a malignant transformation of a rare CD20+ subset of normal T-cells, others suggest that CD20 may act as an activation-induced marker for both benign and malignant T-cells [3]. Regardless of the reason for the presence of CD20, it is difficult to find any evidence that treating a CD20+ PTCL solely with rituximab, a monoclonal antibody targeting CD20, is efficacious; therefore, it is not surprising that our patient showed no response to the treatment. A reliance on more established therapy for PTCL or CTCL may have been better supported. It is likely that the referring physician administered rituximab due to the patient's apprehension concerning systemic cytotoxic chemotherapy and the fact that rituximab is generally considered safe. However, rituximab may disqualify patients from future clinical trials and is not completely innocuous.

Once the patient came under the care of the physicians at The James Cancer Hospital, evidence-based treatments were administered. Although CHOP only provided a transient resolution of the lesions, DD yielded the patient's longest remission to date and significantly improved her quality of life.

The prevalence and characteristics of composite or metachronous T-cell lymphomas have not been well defined. Patients with MF are known to have an increased risk of other lymphoproliferative disorders, such as lymphomatoid papulosis (LyP), cutaneous anaplastic large cell lymphoma (cALCL), Hodgkin's lymphoma, and PTCL. In addition patients with MF may develop large cell transformation, which clinically may behave like a PTCL. Our patient did not have a history of pre-existent pruritic, erythematous rash and presented with localized, nodular skin lesions. Only after about 5 years she developed clinical MF. Clonal relatedness of the initial PTCL and the subsequent MF would require analysis of the size and sequence of the TCR beta fragment amplified by PCR. This analysis has not been performed. Whether the prior history of PTCL or systemic therapy had any influence of the aggressive course of this patient MF in unknown.

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