Prognostic Factors in Primary Cutaneous Anaplastic Large Cell Lymphoma

Characterization of Clinical Subset With Worse Outcome

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**Objectives**: To identify prognostic factors in primary cutaneous anaplastic large cell lymphoma (pcALCL), focusing on extensive limb disease (ELD), defined as initial presentation or progression to multiple skin tumors in 1 limb or contiguous body regions, and to study gene expression profiles of patients with pcALCL.

**Design**: Retrospective cohort study.

**Setting**: The Stanford Comprehensive Cancer Center and dermatology ambulatory clinics.

**Patients**: A total of 48 patients with pcALCL evaluated from 1990 through 2005.

**Main Outcome Measures**: Hazard ratios (HRs) for prognostic factors for overall survival (OS) and disease-specific survival (DSS) and risk factors for progression to extracutaneous disease were identified using Cox regression. Gene expression profiles of 9 typical pcALCL and 3 ELD samples were investigated using complementary DNA microarrays.

**Results**: Univariate analysis demonstrated age, ELD, and progression to extracutaneous disease as significant prognostic factors for OS, whereas ELD and progression to extracutaneous disease were significant for DSS. In multivariate analysis, age (HR, 1.83; 95% confidence interval [CI], 1.02-3.26) and progression to extracutaneous disease (HR, 6.42; 95% CI, 1.39-29.68) remained significant for OS, whereas ELD (HR, 29.31; 95% CI, 1.72-500.82) and progression to extracutaneous disease (HR, 13.12; 95% CI, 1.03-167.96) remained independent prognostic factors for DSS. Presentation with T3 disease was a risk factor for progression to extracutaneous disease (HR, 10.20; 95% CI, 1.84-56.72). Microarray data revealed that patients with ELD and typical pcALCL formed distinct clusters.

**Conclusions**: Patients with ELD have a more aggressive course associated with a differential gene expression profile. More aggressive treatments may be indicated for patients with ELD and those whose disease progresses to extracutaneous disease because they have poorer outcomes.

tors in pcALCL. A secondary aim was to determine if the 2 subgroups have distinct gene expression profiles underlying their differences in clinical behavior and to identify markers that may serve as diagnostic or prognostic markers as well as potential therapeutic targets.

Figure 1. Patients with extensive limb disease (ELD). A, Patient with ELD with T2c involvement of the left lower leg. B, Another patient with ELD with T2c disease involving the entire left leg with edema secondary to irradiation and deep lesions affecting lymphatic drainage.

PATIENT SELECTION

This study was a retrospective analysis of patients with a diagnosis of pcALCL who were evaluated at Stanford University Medical Center, Stanford, California, from January 1990 through December 2005. The clinical and pathological definition of pcALCL used in our study is consistent with that of the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas.1 Patients with extracutaneous disease at presentation, CD30+ large cell transformation of mycosis fungoides (MF), and LyP or borderline diagnoses were excluded. All patients underwent staging studies according to the recommendations by the International Society for Cutaneous Lymphomas (ISCL)-EORTC, including complete blood cell count, comprehensive blood chemistry measurements including lactate dehydrogenase (LDH), and appropriate imaging studies.3 The study was approved by the Stanford University institutional review board.

CLINICAL PROGNOSTIC FACTORS AND DEFINITIONS

Potential clinical prognostic factors evaluated included age at diagnosis, sex, T classification at diagnosis, ELD, presence of spontaneous regression, lesion site, and progression to extracutaneous disease. Routinely collected data, including LDH and Eastern Cooperative Oncology Group (ECOG) performance status, were not included because prognostic factors such as LDH were within reference range for all patients, and ECOG status was 1 for a single patient and 0 for all other patients. All patients were reclassified according to the ISCL-EORTC TNM classification system for primary cutaneous lymphomas other than MF and Sézary syndrome as follows:

- **T1:**
  - Solitary skin involvement
    - T1a, a solitary lesion 5 cm or less in diameter
    - T1b, a solitary lesion more than 5 cm in diameter
- **T2:**
  - Regional skin involvement
    - T2a, all disease encompassing a circular area 15 cm or less in diameter
    - T2b, all disease encompassing a circular area larger than 15 cm but no more than 30 cm in diameter
    - T2c, all disease encompassing a circular area larger than 30 cm in diameter
- **T3:**
  - Generalized skin involvement
    - T3a, multiple lesions involving 2 noncontiguous body regions
    - T3b, multiple lesions involving at least 3 body regions

We defined ELD as presentation with or progression to T2b or T2c tumor involvement of a single limb, or T3b involvement of at least 3 contiguous body regions, including a single limb (Figure 1). For the interest of this article, patients with pcALCL who do not have ELD will be referred to as those with "typical pcALCL." Presence of spontaneous regression was defined as complete resolution of skin lesions without treatment.

Clinical complete response (CCR) was defined as complete resolution of skin lesions with treatment. Relapse rates were calculated among patients who achieved CCR to initial therapy. Relapse was defined as the appearance of any new skin or extracutaneous disease after CCR. All relapses were confirmed by biopsy and histopathologic evaluation. Follow-up information was recorded until January 1, 2006.

STATISTICAL ANALYSIS

All patients were included in the overall survival (OS) and disease-specific survival (DSS) analysis. In OS analysis, events were defined as death resulting from any cause. In DSS analysis, events were defined as death resulting from disease, including complication of treatment. Actuarial survival curves were calculated from the date of diagnosis and plotted using the Kaplan-Meier technique. Differences between subgroups of each variable were compared using the log-rank test. Bonferroni correction was used for pairwise comparisons of variables with more than 2 categories. Univariate Cox regression was performed to identify variables predictive of increased all-cause or disease-specific mortality rates. Multivariate Cox regression was performed using significant univariate variables. For Cox regression, age was treated as a continuous variable and progression to extracutaneous disease as a time-dependent variable. P < .05 was considered to be statistically significant. All P values correspond to 2-sided significance tests, and 95% confidence intervals (CIs) were obtained using standard methods.

Clinical characteristics of patients with and without ELD were compared using Fisher exact test for categorical variables and 2-sample t test for continuous variables. Variables with statistically significant differences were adjusted for in the multivariate model. Cox regression was used to identify risk factors for progression to extracutaneous disease. All analyses were performed using SAS statistical software (version 9.1.4; SAS Institute Inc, Cary, North Carolina).

MICROARRAY PROCEDURES AND GENE EXPRESSION DATA ANALYSIS

All frozen tumor tissue was obtained from the lymphoma tissue bank in the Department of Pathology, Stanford University. Total...
RNA was isolated from frozen tumor tissue according to the manufacturer’s instructions (Invitrogen; Life Technologies, Carlsbad, California) and cleaned using the QIAamp RNA Mini Protocol (Qiagen, Valencia, California). A universal Human Reference RNA (Stratagene, La Jolla, California) was used for comparative hybridization. A total of 2 µg of tumor RNA from each sample and of reference RNA were subjected to 1 round of RNA amplification (RiboAmp Kit; Arcturus, Mountain View, California), and 3 µg of each tumor and reference antisense RNA was reverse transcribed using 9 µg of pd(N)6 random hexamer primer (American Biosciences, Piscataway, New Jersey). Each Cy3-labeled experimental complementary DNA (cDNA) probe was combined with the Cy3-labeled reference probe, and the mixture was hybridized to spotted cDNA microarrays containing 42,000 spots; cDNA microarrays were obtained from the core microarray facility at Stanford.

The fluorescence ratio for each gene spot on the hybridized arrays was obtained with a GenePix 4000 scanner (Axon Instruments, Foster City, California) and analyzed with GenePix 3.0 software (Axon Instruments). Uninterpretable spots were manually flagged and excluded. Hierarchical clustering with array-weighted average linkage clustering and significance analysis of microarrays were applied to identify genes differentially expressed between patients with typical pcALCL and those with ELD.

For cluster analysis, all nonflagged spots with fluorescence intensity greater than 1.5-fold of the local background of the red or green channel were included. Fluorescence ratios were centered for each gene by subtracting (in log space) the median ratio observed across all samples. Genes that were at least 3-fold upregulated or downregulated relative to the median in at least 2 arrays and that passed these filter criteria in 80% of the hybridized arrays were included.

RESULTS

PATIENT DEMOGRAPHICS

A total of 48 patients were included in this study, of whom 25 had been included in a prior study. There were 39 men and 9 women with a mean age at presentation of 54 years. Most patients (n = 30 [63%]) presented with T1 (solitary) disease with similar involvement of the head and neck (n = 10), the trunk (n = 9), and the extremities (n = 11). Of the 10 patients with T2 (regional) disease (21%), 3 had regional involvement of the head and neck, 2 of the trunk, and 5 of the extremities. Eight patients (17%) presented with T3 (generalized) disease. The ELD subgroup (n = 4) is characterized by a significantly older age at presentation with median age of 73 years for ELD vs 48 years for typical pcALCL (P = .01). Similar to the entire cohort, a male predominance (3 of 4) was observed in the ELD subgroup.

TREATMENT AND CLINICAL RESPONSE

The most common local therapies used were excision and radiation therapy, either alone or in combination. The systemic therapies used were chemotherapy alone or in combination with excision or local radiation therapy. The most common chemotherapy regimens were cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (CHOP) and cyclophosphamide, vincristine sulfate, and prednisone (CVP). One patient opted for observation.

The overall CCR and relapse rates following initial therapy were 74% and 46%, respectively. For patients with T1 disease, 73% had local therapy, whereas the remaining patients received systemic therapy. Compared with systemic therapy, local therapy had a higher CCR rate (91% vs 57%) and lower relapse rate (38% vs 75%). The CCR and relapse rates to excision alone and radiotherapy alone were the same. For T2 disease, 5 patients received local therapy, with 4 achieving CCR and 1 patient with subsequent relapse. The other 5 patients received systemic therapy, with 2 achieving sustained CCR without relapse.

Patients with T3 disease, of 6 (67%) achieved CCR after initial chemotherapy (3 CHOP, 1 chlorambucil plus prednisone), but the relapse rate was 100%. One patient received local radiation but had progressive disease. He was then treated with anti-CD30 antibody with short-lived CCR, and subsequently achieved sustained CCR to methotrexate. The disease of 1 patient who opted for observation progressed to nodal involvement, and he achieved CCR when treated with chemotherapy with local radiation. Owing to our small sample size, we do not have conclusive evidence to advocate that any specific therapy is superior.

Patients with ELD (n = 4) were characterized by a lack of durable response to treatment. With the exception of 1 patient who was initially disease-free for 2.5 years following excision and local radiation, the disease of all patients progressed regionally within 3 months of completing chemotherapy (n = 2) or local radiation (n = 1). These patients also failed salvage treatments, including various chemotherapy regimens, oral bexarotene, interferon alfa-2b, local radiation, and topical mechlorethamine hydrochloride. Chemotherapy regimens used included CHOP, CVP, CEPP, VACOP-B, methotrexate, and gemcitabine hydrochloride. The CCR rate to initial therapy for patients with ELD was 25% (1 of 4) compared with 79% (34 of 43) in patients without ELD (P < .05).

LONG-TERM OS AND DSS

Patients were followed up for a median of 4 years (range, 0.6-15.1 years). The median OS and DSS had not been reached. The OS and DSS rates were 76% and 85% at 5 years and 70% and 85% at 10 years, respectively (Figure 2). By the end of the study follow-up period, 10 patients had died. Five of these 10 patients died of pcALCL: 3 had ELD, the disease of 1 had progressed to regional lymph node involvement and 1 to spinal involvement. Others died of unrelated causes, including 2 of chronic lymphocytic leukemia, 2 of cardiac disease, and 1 from suicide.

UNIVARIATE AND MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS

The 5-year OS and DSS rates of subgroups of each prognostic factor and their corresponding P values are shown in Table 1. Patients with ELD had significantly worse OS and DSS than those patients without ELD (P = .01 and < .001, respectively). Patients diagnosed at age 54 years or older had significantly worse OS (P = .04) but no significant differences in DSS (P = .15). Patients with T1 dis-
ease had a more favorable OS and DSS compared with those with T2 and T3 disease, although the differences were not significant (see Table 1 for P values). Sex, presence of spontaneous regression, lesion site, and progression to extracutaneous disease were not significantly associated with OS or DSS (see Table 1 for P values).

These potential prognostic factors were also analyzed using Cox regression. Each 10-year increase in age at presentation resulted in an approximately 2-fold increase in risk of both the all-cause mortality rate (HR, 1.99; 95% CI, 1.15-3.44) and disease-specific mortality rate (HR, 2.20; 95% CI, 0.95-5.11). Of note, treating progression to extracutaneous disease as a time-dependent variable, it was found to be a significant prognostic factor for both all-cause and disease-specific mortality (HR, 6.53; 95% CI, 1.59-26.80; HR, 6.95; 95% CI, 1.15-42.15, respectively). Otherwise, results showed the same conclusions as Kaplan-Meier survival analysis.

In multivariate analysis, age at diagnosis and progression to extracutaneous disease were found to be significant independent predictors for all-cause mortality (P = .04 and .02, respectively; Table 2). For disease-specific mortality, ELD and progression to extracutaneous disease were found to be independent prognostic factors (P = .02 and <.05, respectively).

DISEASE PROGRESSION TO EXTRACUTANEOUS DISEASE

Eight of our 48 patients with pcALCL experienced disease progression to involve extracutaneous sites. Six patients’ disease progressed to N1M0 disease involving a draining lymph node region. For the 2 patients whose disease progressed to visceral involvement, 1 developed spinal involvement, and 1 patient’s disease progressed to involvement of a draining lymph node region and the parotid. Patients with ELD did not have a greater risk of their disease progressing to extracutaneous disease (P = .53). The only significant risk factor for progression to extracutaneous disease was T classification at diagnosis. Compared with patients with T1 disease, those with T3 disease at diagnosis had a significantly higher risk of progression (HR, 10.20; 95% CI, 1.84-56.72). In our study, the disease of 50% of those with T3 disease initially (2 with T3a disease, 2 with T3b disease) progressed to extracutaneous involvement. The median time to progression was 8 months (range, 4 months to 7.4 years).

GENE EXPRESSION PROFILES

A total of 14 biopsy samples were available for gene expression profiling. Figure 3A depicts 1213 unique cDNA elements that were used for hierarchical cluster analysis of tumor tissue samples from 7 patients with typical pcALCL (9 samples, 2 patients with 2 separate biopsy samples) and 3 with ELD (5 samples, 2 analyzed in duplicate). Biopsy samples taken from the same patient or samples performed in duplicate clustered next to each other. Two groups, based on the first bifurcation in the array dendrogram, could be identified that correlated with clinical data: typical pcALCL cases clustered on the left, whereas the ELD cases clustered on the right of the dendrogram (Figure 3A).

The gene expression map further illustrates that several independent sets of genes are responsible for the pcALCL substructure. One of the clearest distinctions involves genes related to the epidermis, such as keratins. No morphologic differences in the hematoxylin-eosin-stained sections between the 2 groups were found that could account for the differential of epidermal genes. After subtraction of 461 genes highly expressed in normal epidermis that were identified using a nonparametric t test, the segregation of the 2 groups remained identical (data not shown).

Genes highly expressed in typical pcALCL were associated with the T-cell receptor (TRA@), T-cell surface marker (CD6), T-cell function and dendritic cell function (ADAMDEC1, CD1C), cell proliferation (SIAT9, FGFR1, CD81, DUSP6), remodeling of the extracellular matrix (MMP9), immune response and signal transduction (APBB1IP, CSF2RB, ICAM1P1, CCL19, LTB), and with drug response to retinoids (RXRA [GenBank NM_002957]) and to alemtuzumab (IgG against CDW52, CD52) (Figure 3B).

Only a small group of upregulated genes were identified that characterize the ELD subtype (Figure 3C). Three of these genes (STAT5A [GenBank NM_003152], HIPK2, and HBA2) have been described as being involved in apop-
Table 1. Overall Survival (OS) and Disease-Specific Survival (DSS) Rates for Potential Prognostic Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No. (N=48)</th>
<th>5-y OS Rate, %</th>
<th>P Valuea</th>
<th>5-y DSS Rate, %</th>
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<td>Extremities (T1/T2)</td>
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<td>Head and neck (T1/T2), trunk (T1/T2), or generalized (T3)</td>
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<td>Progression to extracutaneous disease</td>
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Abbreviation: ELD, extensive limb disease.
a Log-rank test.
b Bonferroni-corrected P values; T1 and T2 are compared.
c Bonferroni-corrected P values; T1 and T3 are compared.
d Bonferroni-corrected P values; T2 and T3 are compared.
e Two-year OS and DSS are presented because 5-year data are unavailable.

Table 2. Adjusted Hazard Ratios (HRs) From Multivariate Cox Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-Cause Mortality</th>
<th>Disease-Specific Mortality</th>
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</thead>
<tbody>
<tr>
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<td>HRa (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age at diagnosis (per 10 y)</td>
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</tr>
<tr>
<td>ELD</td>
<td>3.48 (0.72-16.74)</td>
<td>.12</td>
</tr>
<tr>
<td>Progression to extracutaneous diseaseb</td>
<td>6.42 (1.39-29.68)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ELD, extensive limb disease.
a Adjusted for other variables listed.
b Treated as time-dependent variable.

To our knowledge, this is the largest single-center study to date investigating prognostic factors in pcALCL in the United States. Overall, the clinical characteristics of our 48 patients are consistent with those of previous studies at other institutions worldwide, confirming that pcALCL as a group is associated with a favorable prognosis.2,3,15-17 However, to our knowledge this is also the first report that describes a subset of patients with ELD who had a worse treatment and survival outcome compared with patients with pcALCL but without ELD (typical pcALCL).

Despite the small sample size, ELD was found to be a significant prognostic factor for DSS, with a 2-year DSS of 50% in ELD compared with 93% in the typical pcALCL cohort (P < .001). The patients with ELD differed from patients with typical pcALCL in that they presented at a significantly older age (P = .01). They are also characterized by rapid progression of skin disease, usually with rapid development of multiple tumor nodules extending in the same region or limb, with a significantly lower clinically complete response rate to initial therapy (P = .05) and lack of

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durable response to treatment. However, the worse prognosis in ELD is not explained by patient age or progression to extracutaneous disease when these factors are controlled in the analysis.

Age at diagnosis has not been found to be a significant prognostic factor in prior studies. Our findings may be related to the fact that age was treated as a continuous variable rather than a categorical variable in statistical analyses, which allowed for increased power in our analysis.2,15 The fact that age was a significant prognostic factor for OS but was not significant for DSS suggests that the survival differences may largely be attributable to deaths caused by age-associated illness. The other finding that patients with T1 disease or solitary lesions showed

Figure 3. Hierarchical clustering dendrogram and gene signatures from cluster analysis of 14 samples of primary cutaneous anaplastic large cell lymphoma (pcALCL). Included are 9 samples of typical pcALCL and 5 of extensive limb disease (ELD). Each row represents a separate complementary DNA clone on the microarray and each column represents a separate tissue sample. Red, green, and black squares indicate that the expression of genes is greater than, less than, or equal to the median level of expression across all 14 tissue samples, respectively. Gray represents missing or poor-quality data. A, Overview hierarchical clustering dendrogram showing 2 distinct groups based on the first bifurcation: the typical pcALCL cases (lilac) on the left, and the ELD cases (blue) on the right. Control samples from normal skin (green) are shown on the left for comparison. B, The lilac bar illustrates genes that are overexpressed in the typical pcALCL group. C, The blue bars illustrate 2 small groups of genes that show overexpression in the ELD group.
a trend toward better prognosis is consistent with findings from previous studies. Evidence for progression to extracutaneous disease as a predictor for mortality has been conflicting. In this study, progression to extracutaneous disease was found to be a significant predictor of worse OS and DSS. One reason for these findings may be that 2 of our 8 patients whose disease progressed to extracutaneous disease had visceral involvement, which may have a worse prognosis than involvement of draining lymph node(s) as in other studies. Another reason may be that progression to extracutaneous disease was treated as a time-dependent variable, which to our knowledge was not performed in prior studies. The finding that patients with T3 disease have a higher risk of progression to extracutaneous disease confirms a trend that has previously been observed.

Some examples of genes that were found to be upregulated in ELD are STAT5A and IL2RA. The IL2R/STAT5 signaling pathway plays an important role in regulating T-cell activation. One of the major effects of IL2R signal transduction is the activation of latent cytoplasmic transcription factors known as STAT (signal transducer and activator of transcription). Improper regulation, especially constitutive activation of STAT5, directly contributes to oncogenesis through stimulation of cell proliferation and prevention of apoptosis. Activation of the IL2R/STAT5 pathway in CTCL, including cutaneous ALCL, has been described previously. One hypothesis based on our data is that ELD may be more aggressive clinically than typical pcALCL owing to the aberrant activation of the IL2R/STAT5 pathway. Denileukin diftitox is an IL2R-directed-fusion protein armed with diphtheria toxin that may be relevant in the treatment of ELD, and it has led to complete response in a case of pcALCL. STAT5A may represent another target molecule for therapeutic intervention. Deacetylase activity has been shown to be required for activation of transcription by STAT5, and thus inhibition of deacetylase activity represents a promising therapeutic intervention in STAT5-associated cancers. Vorinostat, an oral histone deacetylase inhibitor (HDAC-i), has recently been approved for treatment of CTCL. Another HDAC-i, depsipeptide (FK228, romidepsin), has also demonstrated activity in CTCL, and clinical trials are under way.

Genes that were downregulated in ELD include retinoid X receptor alpha (RXRA). Bexarotene, an RXR ligand that selectively binds and activates RXR subtypes, has been shown to induce apoptosis of malignant T cells and has demonstrated activity in CTCL. The lack of RXRA gene expression in ELD may explain therapeutic resistance to bexarotene in this subgroup. Of the patients with ELD in the study, I received bexarotene and failed to respond.

Further studies of these potential therapeutic targets may aid in the treatment of patients with ELD whose disease is refractory to currently used treatment regimens. In contrast, therapy for solitary lesions is well delineated. radiotherapy and simple excision, used individually or in combination, are acceptable. In our patients with T1 disease, no notable differences were seen between local and systemic treatments, with local treatment showing a higher CCR rate and lower relapse rate. Our data also support using local treatment as first-line therapy for T1 disease.

Combination chemotherapy had previously been thought to be the most appropriate first-line treatment for generalized disease. However, recent data suggest that patients with generalized skin lesions can be treated with radiotherapy if the number of skin lesions is limited. Patients who develop extracutaneous disease and those who are more symptomatic or have progressive skin disease can be treated with methotrexate, systemic biologic or targeted therapy (bexarotene, interferons, denileukin diftitox), or doxorubicin-based chemotherapy. One of the reasons for using a differential approach based on symptom or disease severity is the increased frequency of relapse in patients treated with traditional chemotherapy. Similar findings were observed in this study, with all 4 of our patients with T3 disease who achieved CCR with chemotherapy subsequently relapsing.

Alternative therapeutic interventions that have been suggested include anti-CD30 monoclonal antibodies and stem cell transplantation. Data on these treatments are currently very limited. Two patients with multiple relapses opted for autologous hematopoietic stem cell transplantation as salvage therapy, and both experienced recurrence of disease within 2 months after transplant. Further studies with long-term follow-up are needed to fully evaluate these alternative therapies.

In view of the results of our prognostic analysis and prior studies, we propose the following recommendations for appropriate treatment of patients with pcALCL. Two subgroups, typical pcALCL and ELD, can be distinguished. On the one hand, patients with typical pcALCL have an excellent prognosis. Patients with T1 (solitary lesion) or limited T2 (typical regional) diseases should be treated primarily with local therapies such as radiotherapy or excision. Patients with limited multifocal (T3) disease can be treated with skin-directed therapies as well. Patients who fail skin-directed options or have extensive generalized disease should be considered for systemic therapy. On the other hand, patients with ELD have an aggressive course with worse prognosis and short-lived responses with traditional therapy, including radiotherapy. Optimal treatment for these patients remains to be defined; however, we recommend considering systemic therapies upfront with or without consolidative radiotherapy. Our preliminary gene expression data suggest that denileukin diftitox or HDAC-i may result in favorable antitumor response.

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Author Contributions: Drs Woo and Kim had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Woo, Jones, Vanoli-Storz, Kohler, Reddy, Advani, Hoppe, and Kim. Acquisition of data: Woo, Jones, Vanoli-Storz, Kohler, Reddy, Advani, Hoppe, and Kim. Analysis and interpretation of data: Woo, Jones, Vanoli-Storz, Kohler, Hoppe, and Kim. Drafting of the manuscript: Woo, Jones, and Vanoli-Storz. Critical revision of the manuscript for important in-

15. Li HL, She ZG, Li TB, et al. Overexpression of myofibrillogenesis regulator-1 agonists: a valid and effective

16. Calzado MA, Renner F, Roscic A, Schmitz ML. HIPK2: a versatile switchboard regulating the transcription


of cell growth by IL-2: role of STAT5 in protection from apoptosis but not in cell cycle progression. J

transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from


22. Marks PA, Breslow R. Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor

23. Renner F, Roscic A, Schmitz ML. HIPK2: a versatile switchboard regulating the transcription

transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from

25. Marks PA, Richon VM, Breslow R, Rifkind RA. Histone deacetylase inhibitors as new cancer drugs. Curr