19 Syndromes and Clinical Management Issues Associated with T-Cell Lymphomas

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Introduction

T-cell lymphomas have been associated with specific clinical syndromes and characteristics, often requiring special attention by the clinician. In addition, some of the drugs used to treat T-cell malignancies have specific side effects or distinctive risks associated with their use. In this chapter, we will review some of the unique clinical syndromes that may occur in patients with T-cell lymphomas, either as a result of the disease or as a result of the treatments for the malignancy.

Clinical Syndromes

Poor Prognosis

Lymphomas derived from T-lymphocytes have been associated with the presence of more adverse features and a worse prognosis than lymphomas of B-cell origin [1–4]. Retrospective evaluation of patients enrolled in two GELA (Groupe d'Etude des Lymphomes Aggressives) studies has yielded data on the implication of the T-cell phenotype on prognosis [1, 2]. While adverse features are more likely to be present in patients with T-cell lymphomas, it appears that the T-cell histology itself is an independent poor prognostic factor [2, 3].

Of 361 patients with lymphoma treated on the LNH-84 regimen for aggressive lymphoma, 108 had peripheral T-cell lymphoma and 253 had B-cell lymphomas [1]. When compared to patients with B-cell lymphomas, those with peripheral T-cell lymphomas were more likely to have stage IV disease (53% vs. 45%) and B-symptoms (58% vs. 42%). In addition, those with T-cell histology had a higher rate of relapse (43% vs. 29%) and a shorter freedom-from-relapse survival (34 months vs. not reached). Overall survival was shorter in the patients with T-cell lymphomas (42 months vs. 50 months); however, this difference was not statistically significant.

The multicenter LNH-87 trial enrolled patients with intermediate- or high-grade non-Hodgkin's lymphoma, and Gisselbrecht et al. reported on the prognostic significance of the T-cell phenotype in patients treated on that protocol [2]. Of 1,883 evaluable patients, 288 (15%) had peripheral T-cell lymphomas and 1,595 (85%) had B-cell lymphomas. While B-cell lymphoma patients had more bulky disease (41% vs. 26%), T-cell lymphoma patients had more bone marrow involvement (31% vs. 17%) and advanced stage disease (78% vs. 58%). Peripheral T-cell lymphoma patients were also more likely to have B-symptoms (57% vs. 40%) and increased B2-microglobulin (50% vs. 34%) than those with

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B-cell lymphomas. Complete remission rates (54% vs. 63%), 5-year overall survival rates (41% vs. 53%), and event-free survival rates (33% vs. 42%) were worse for patients with T-cell lymphomas compared to B-cell lymphomas.

Investigators at the M. D. Anderson Cancer Center reviewed six front-line chemotherapy clinical trials in aggressive non-Hodgkin's lymphoma that were performed at the institution from 1984 to 1995 [3]. Of 560 evaluable patients, 492 (88%) were of B-cell phenotype and 68 (12%) were peripheral T-cell lymphomas. The 5-year overall survival rate for those patients with peripheral T-cell lymphomas was 38% compared to 55% for those with B-cell lymphomas. T-cell lymphoma patients with an International Prognostic Index (IPI) score of more than two (poor prognosis) had a 5-year overall survival of 10% compared to 40% ($p=0.011$) in those patients with B-cell lymphomas. T-cell lymphoma patients with an M. D. Anderson prognostic tumor score (MDATS) of more than two (poor prognosis) had a 5-year overall survival of 24% compared to 41% ($p=0.02$) in those with B-cell lymphomas. Multivariate analysis confirmed that the most significant independent predictors of overall survival were the MDATS, the IPI score, and the T-cell phenotype.

Hemophagocytic Syndrome

The hemophagocytic syndrome (HPS) is characterized by fever, pancytopenia, hepatosplenomegaly, and liver dysfunction. The clinical syndrome results from activated macrophages, and evidence of hemophagocytosis can be found in the bone marrow and other tissues. HPS has been associated with T-cell lymphomas [5–7]. While the syndrome has been associated with the Epstein–Barr virus, malignancy-associated HPS such as that found in patients with T-cell lymphomas is not necessarily due to viral infection [6, 8]. Diagnostic criteria have been established for HPS, mostly arising from literature on the familial form of the disease [9]. Five out of the following eight criteria are required to make a diagnosis of HPS: (1) fever; (2) splenomegaly; (3) cytopenias in at least two cell lines; (4) hypertriglyceridemia and/or hypofibrinogenemia; (5) ferritin more than 500 mg/L; (6) decreased or absent NK-cell activity; (7) sCD25 more than 2,400 U/mL; (8) hemophagocytosis documented in the bone marrow, cerebrospinal fluid, or lymph nodes [9].

Lymphoma-associated HPS was evaluated in a retrospective series of 29 patients treated between 1994 and 2006 [10]. The authors found that of the 29 patients with HPS, 11 patients (37.9%) had aggressive NK/T-cell leukemia; 8 (27.6%) had peripheral T-cell lymphoma, not otherwise specified (NOS); 3 (10.3%) had extranodal NK/T-cell lymphoma, nasal type; and 2 patients (6.9%) had anaplastic large cell lymphoma (ALCL). Just 17% (five patients) had diffuse large B-cell lymphoma. In comparison to those patients with B-cell lymphoma-associated HPS, those patients with T- or NK-cell malignancies were more likely to be younger than 60, have evidence of disseminated intravascular coagulation (DIC), and have bone marrow involvement. For all patients, the most frequent symptom was fever (100%) followed by hepatosplenomegaly (93.1%). Of the 23 patients who received combination chemotherapy for their malignancy, four achieved a complete remission and three achieved partial remission. The median survival of all patients was 36 days (range 2 to 1,991+ days). Univariate analysis revealed that poor prognostic factors included poor performance status, the presence of jaundice, the presence of DIC, poor response to therapy, and T- or NK-cell lymphoma.

More evidence supporting the poor prognosis of T-cell lymphoma-associated HPS comes from a review of 113 patients with aggressive T-cell lymphoma of whom 28 had HPS [11]. Fever was identified in 100% of the 28 patients with HPS and in 48% of those without HPS. Hepatosplenomegaly was identified in 100% of the patients with HPS compared to 39% of those without HPS. Cytopenias in more than one cell line (100% vs. 20%) and bone marrow involvement (57% vs. 32%) were also more likely to be present in the T-cell lymphoma patients with HPS. Patients were treated with combination chemotherapy. Eleven of the 28 patients with T-cell lymphoma associated HPS

died of multiorgan failure prior to receiving chemotherapy. The median survival of the HPS group was 40 days compared to a median survival of 8 months in those without HPS.

Tong et al. recently reviewed data from 173 patients diagnosed with peripheral T-cell lymphoma to assess the role of bone marrow involvement in the prognosis and outcome of the disease [12]. In their evaluation, 70 of the 173 patients (40%) with peripheral T-cell lymphoma had bone marrow involvement. Of those patients with bone marrow involvement, the HPS was identified in 36% compared with only 8% of those patients without bone marrow involvement. The highest frequency of bone marrow involvement was found in angioimmunoblastic T-cell lymphoma with 64% having bone marrow involvement. Marrow involvement was also identified in 46% of the peripheral T-cell lymphoma, NOS, patients; in 29% of the anaplastic large T-cell lymphoma patients; in 23% of extranodal NK/T-cell lymphoma patients; and in 13% of patients with enteropathy-type T-cell lymphoma. The diagnosis of HPS was associated with a worse 1-year overall survival in those with bone marrow involvement (5%) than without bone marrow involvement (49%) [12].

Skin Infections

Patients with cutaneous T-cell lymphoma (CTCL) are at risk for morbidity and mortality from infection caused by bacterial and viral pathogens. In a retrospective cohort study of 356 patients with mycosis fungoides or Sézary syndrome, infection was noted to be an important cause of morbidity [13]. The most common infections were cutaneous bacterial infections which accounted for 17 infections per 100 patient years. Following cutaneous bacterial infections were cutaneous herpes simplex and herpes zoster virus infection (3.8 infections per 100 patient-years), bacteremia (2.1 infections per 100 patient-years), bacterial pneumonia (1.7 infections per 100 patient-years), and urinary tract infections (1.4 infections per 100 patient-years). Twenty-seven patients (36%) in the cohort died from infection, and pneumonia or bacteremia was present in 88% of those who died of infection. Using regression models, the most important risk factor for recurrent bacterial skin infection, disseminated herpes virus infection, bacteremia, and death from infection was the presence of advanced stage (stages III and IV) of the lymphoma.

Tokura et al. have demonstrated that circulating Sézary cells have a response to bacterial superantigens, such as the toxins produced by *Staphylococcus aureus*—exfoliating toxin (ExT), staphylococcal enterotoxins (SE), and toxic shock syndrome toxin-1 (TSST-1) [14]. In two patients with CTCL whose skin was colonized with *S. aureus*, treatment with antibacterial agents lessened the severity of CTCL-associated skin manifestations and eliminated the *S. aureus* [15]. Peripheral blood mononuclear cells (PBMC)—which contained a high proportion of circulating Sézary cells—taken from one of the patients demonstrated marked proliferation when exposed to staphylococcal exotoxin. Superinfections of the skin with *S. aureus* may play a role in the exacerbation of the disease course of CTCL.

Two recent studies have provided data on the rates of *S. aureus* colonization in patients with CTCL [16, 17]. In the first study, researchers at Northwestern University prospectively evaluated 50 patients with CTCL, 25 patients with psoriasis to serve as controls, and 25 healthy control patients [16]. *S. aureus* colonization was identified in 44% of the CTCL patients, 48% of those patients with psoriasis, and in 28% of healthy controls. Because of small sample size, no significant difference was identified in the rates among groups. Higher rates of methicillin-sensitive *Staphylococcus aureus* (MSSA) colonization were identified in CTCL patients (42%) compared to healthy controls (20%); however, this difference only trended toward statistical significance.

In the second and larger study, Talpur et al. performed skin and nares cultures in a prospective manner in 106 patients with newly or recently diagnosed mycosis fungoides or Sézary syndrome [17]. Patients with positive nasal cultures were treated with topical nasal mupirocin to suppress colonization, and those with positive skin

cultures received oral antibiotics. Sixty-seven patients (63%) had skin colonization with *S. aureus*, and 57 patients (54%) had nasal colonization with the bacteria. The highest rates of colonization were seen in patients with erythrodermic Sézary syndrome (48%), and the lowest rates were seen in CTCL without erythroderma (26%). Historical data used for comparison revealed that the *S. aureus* colonization rate seen in atopic dermatitis is 64%. The colonization rate in psoriasis is 21%, and the rate in the general population is 10% [17]. Eradication of the bacterial colonization with oral or topical antibiotics reduced the *S. aureus* colonization by 85–91%, and over half of those treated experienced clinical improvement in their disease symptoms [17].

Fatigue and Edema in Cutaneous T-Cell Lymphoma

Patients with CTCL may have increased rates of peripheral edema and fatigue. Negro-Vilar et al. presented preliminary data from the phase III, double-blind, placebo-controlled trial of denileukin diftitox in patients with CTCL and demonstrated that denileukin diftitox was superior to placebo [18]. Eighty-six percent (124 of 144 patients randomized) had received one or more prior treatment regimens, including single agent chemotherapy, systemic retinoids, phototherapy, or external beam radiotherapy. While there was a higher rate of adverse events in the experimental arms, there was also noted to be a relatively high percentage of patients experiencing fatigue and peripheral edema in the placebo arm. Peripheral edema was experienced by patients in the denileukin diftitox 9-μg/kg arm (20%) and in the 18-μg/kg arm (25.5%); in the placebo arm, the rate was 22.7%. Fatigue was noted both in the 9 μg/kg arm (46.7%) and in the 18 μg/kg arm (43.6%); the fatigue rate in the placebo arm was 31.8%.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a well-known oncologic emergency that may occur in patients with aggressive hematologic malignancies upon the initiation of cytotoxic chemotherapy. Cairo and Bishop defined two types of TLS—laboratory TLS and clinical TLS—in their 2004 publication on the subject [19]. Laboratory TLS was defined as having at least two serum lab values with the following abnormalities: potassium ≥6.0 mmol/L; uric acid ≥8 mg/dL, phosphate ≥4.5 mg/dL in adults or ≥6.5 mg/dL in children, calcium ≤7 mg/dL. Having laboratory TLS plus one clinical manifestation (increased serum creatinine concentration ≥1.5 times upper limit of normal, cardiac arrhythmia/sudden death, or seizure) characterized clinical TLS. These defining features of TLS must be present within 3 days before or 7 days after the initiation of chemotherapy.

There is a paucity of literature available on the incidence of TLS in T-cell malignancies. TLS has been reported in peripheral T-cell lymphoma and in ALCL [20–23]. There have been at least three case reports of TLS occurring after initiation of corticosteroid monotherapy in T-cell lymphoblastic lymphoma [24–26]. The first case reported was a patient with untreated T-cell lymphoblastic lymphoma who received two doses of hydrocortisone prior to a platelet transfusion who subsequently developed laboratory TLS [25]. A 20-year-old man with T-cell lymphoblastic lymphoma developed acute renal failure requiring hemodialysis after receiving prednisolone [26]. A recently reported case involved a 60-year-old woman who received dexamethasone for her diagnosis of precursor T-lymphoblastic lymphoma/leukemia and subsequently developed laboratory evidence of TLS, also requiring hemodialysis [24].

TLS has recently been reported in human T-lymphotropic virus (HTLV)-1 adult T-cell leukemia/lymphoma (ATLL). A 49-year-old woman with an 8-year history of systemic lupus erythematosus (SLE) was diagnosed with HTLV-1-associated ATLL after presenting with fevers, malaise, and lymphadenopathy [27]. She developed TLS with hyperkalemia, hyperphosphatemia, and hypocalcemia; and she died 3 days after chemotherapy with cyclophosphamide, doxorubicin, and prednisone was initiated. Bouaziz et al. reported their experience with a

50-year-old man with ATLL with skin involvement who later experienced leukemic conversion of the ATLL [28]. When the patient was treated with combination chemotherapy for his disease, he developed skin erosions in the areas of prior cutaneous leukemic infiltration. Histopathological examination of the skin erosions showed atypical T-lymphocytes (CD3+, CD4+, and CD25+) with apoptosis. Because of this skin finding, the authors suggest a new term to describe the entity—"cutaneous tumor lysis" [28].

TLS has been reported in one patient with CTCL. A 65-year-old man with mycosis fungoides had failed therapy with bexarotene and photophoresis when he was admitted for fever and dyspnea [29]. Since a chest X-ray showed bilateral infiltrates, therapy with antibiotics and intravenous corticosteroids was initiated for presumed *Pneumocystis carinii* infection. Over the next 4 days, he developed laboratory evidence of TLS requiring therapy with rasburicase (recombinant urate oxidase).

Central Nervous System Involvement

T-cell lymphomas may manifest as primary central nervous system (CNS) lymphomas, or CNS involvement may occur as a secondary phenomenon resulting from spread of the initial disease site(s). Lymphomas of T-cell histology comprise a minority of the cases of primary and secondary CNS lymphoma; the majority of cases are of B-cell origin [30, 31].

The incidence of primary CNS lymphoma in the United States was 5.1 per one million person-years in 1998 [32]. There are case reports of primary CNS lymphoma of T-cell origin, including individual case reports of primary CNS manifestations of ALCL, adult T-cell lymphoma/leukemia, and extranodal NK/T-cell lymphoma [33–36]. To characterize primary CNS T-cell lymphoma, Shenkier et al. performed a retrospective review of 45 patients from 12 cancer centers in seven countries [37]. The median age of the patients was 60 years (range, 3–84 years), and none of the patients had systemic lymphoma at presentation. Median disease-specific survival was 25 months, and the 5-year disease specific survival was 51%. Good Eastern Cooperative Oncology Group (ECOG) performance status (PS of 0 or 1) and the use of methotrexate were associated with improved outcome.

In addition to presenting with brain involvement, primary CNS lymphoma may also present with leptomeningeal involvement as the primary site of disease [37–39]. Levin et al. reviewed their cases of primary CNS lymphoma treated over the past 10 years [38]. Out of 100 cases, five patients (5%) had lymphomas of T-cell histology. Each of those five patients presented with leptomeningeal involvement rather than brain involvement, and four of the patients had neuronal lymphomatosis at presentation. Each of the five patients had evidence of cranial or peripheral nerve dysfunction. Four of the five died within 10–19 months and one patient was alive at 36 months from the date of report publication.

Primary CNS lymphoma of T-cell origin can be difficult to diagnose and may, in fact, be under recognized [40]. Performing T-cell receptor gene rearrangements on the tumor biopsy samples may increase the accuracy of diagnosis and may distinguish between reactive lymphoid infiltrates [40]. Clinicians might also consider meningeal or nerve biopsy in the setting of symptoms of neuronal lymphomatosis, especially in the setting where cerebrospinal fluid cytology findings are not conclusive [38].

Salzburg et al. evaluated the patterns of secondary CNS involvement in childhood and adolescent non-Hodgkin's lymphoma and found that CNS involvement was associated with advanced stage of lymphoma [31]. CNS involvement was found in 5.9% of 2,381 patients. Among the T-cell lymphoma subtypes, CNS involvement was identified in 3.3% of ALCL cases and in 3.2% of T-cell lymphoblastic lymphoma cases. Other T-cell lymphoma subtypes may spread to the CNS, including NK/T-cell lymphoma and mycosis fungoides. Mycosis fungoides, with or without large cell transformation, has been associated with secondary CNS involvement [41–43]. Nasal-type extranodal NK/T-cell lymphoma may rarely present with primary CNS involvement [36]. More likely is relapse within the CNS or

direct extension from the nasal area into the CNS [44–47]. Hon et al. report a 78-year-old woman who presented with stage IE nasal-type natural killer cell lymphoma with the primary cite of disease located in a left elbow ulceration [45]. Three months later, the patient presented with blurry vision and was found to have bilateral hypopyon. An aqueous tap and lumbar puncture confirmed that NK cells were present, and a computed tomography scan revealed hemorrhagic lymphomatous infiltration. Luther et al. described a 37-year-old man with direct extension of nasal NK/T-cell lymphoma to the brain from the left orbit into the left frontal lobe [47]. Two cases have recently been described of intraocular involvement of NK/T-cell lymphoma, having spread from its nasal- or paranasal site of primary disease [44, 46].

Hypocalcemia and Hypomagnesemia

Low levels of serum calcium and magnesium have been reported in patients with CTCL [48]. In a retrospective review of 80 mycosis fungoides patients evaluated at the M.D. Anderson Cancer Center prior to 2000, the authors found that hypomagnesemia was present in 22.2% of patients with early stage disease (stages I), 38.5% of those with intermediate stage disease (stages II), and 67.5% of those with advanced stage disease (stages III and IV) [48]. Hypocalcemia was found in 8.3% of early stage mycosis fungoides patients, 54.5% of those with intermediate stage disease, and 61% of those with advanced stage disease.

The etiology for these electrolyte disturbances is unclear. One possible explanation for the hypocalcemia is its relation to preexisting magnesium depletion. The release of parathyroid hormone is inhibited under conditions of hypomagnesemia, and this can result in secondary hypocalcemia [49]. Through its role in impairing immune function, magnesium deficiency may play a role in progression of mycosis fungoides [48]. Rats fed a magnesium-deficient diet that subsequently develop hypomagnesemia have been shown to develop T-cell lymphomas [50, 51].

Second Malignancies

CTCL patients are at risk for second malignancies, including malignant melanoma and second lymphomas [52–54]. Pielop et al. reported six cases of malignant melanoma among a database of 250 CTCL patients over a 3-year period [54]. In four of the melanoma cases, the melanoma was diagnosed prior to or concurrent with the diagnosis of CTCL. In the other two patients, dysplastic nevi were noted at the time of the CTCL diagnosis. The prevalence of malignant melanoma in the CTCL population under study was 2.4%, significantly higher than the 0.2% prevalence of melanoma in the general population [54]. Supporting data on the incidence of malignant melanoma in the CTCL population comes from a retrospective review of 285 cases of CTCL in London, England, in which six cases of melanoma were identified [52]. Of those six, four were diagnosed with melanoma after being diagnosed with CTCL, and two were diagnosed with melanoma prior to the CTCL diagnosis. While malignant melanoma was identified in 2.1% of the 285 cases of CTCL being studied, the crude rate of melanoma in the general population in England, London, in 1998 was 8.8/100,000 in men and 11.4/100,000 in women [52].

Huang and collaborators performed a retrospective study of two cohorts to assess the risks for developing second cancers in patients with mycosis fungoides or Sézary syndrome [53]. The first cohort consisted of the nine population-based U.S. cancer registries that make up the Surveillance, Epidemiology, and End Results Program (SEER-9); the second cohort consisted of the Stanford University referral center cohort of cutaneous lymphoma patients. The SEER-9 cohort included patients diagnosed between 1984 and 2001, and the Stanford cohort included those diagnosed between 1973 and 2001. Among the 1,798 CTCL patients that comprised the SEER-9 cohort, there were 197 second cancers diagnosed (standardized incidence ratio [SIR] of 1.32; 95% confidence interval [CI], 1.15–1.52). Patients with CTCL were at significantly increased risk for Hodgkin lymphoma (SIR = 17.14; 95% CI, 6.25–37.26), non-Hodgkin lymphoma

(SIR = 5.08; 95% CI, 3.34–7.38), melanoma (SIR = 2.6; 95% CI, 1.25–4.79), and urinary cancer (SIR = 1.74; 95% CI, 1.08–2.66). Among the 429 patients identified in the Stanford cohort, there were 37 second malignancies diagnosed (SIR = 1.04; 95% CI, 0.76–1.44). The Stanford University CTCL patients were at significantly increased risk for Hodgkin lymphoma (SIR = 27.27; 95% CI, 5.35–77.54) and cancer of the biliary system (SIR = 11.76; 95% CI, 1.51–42.02).

Management Issues Associated with Therapy

In the following section, we will review the unique management issues that exist for a variety of treatments used in T-cell lymphomas. The four FDA-approved drugs for CTCL—denileukin diftitox, bexarotene, vorinostat, and romidepsin—are each associated with distinctive side effect profiles, and these will be reviewed first. The unique features of pralatrexate, the first and only agent approved for peripheral T-cell lymphoma, will then be examined. Finally, we will review some investigational agents which have been demonstrated to have activity in T-cell lymphomas.

Denileukin Diftitox

Denileukin diftitox (DAB389IL; Ontak®) is a genetically engineered fusion protein that combines parts of the diphtheria toxin with the interleukin-2 (IL-2) receptor-binding domain. Denileukin diftitox has been shown to have activity in lymphoid malignancies. In 1999 the drug was granted approval by the FDA for the treatment of CTCL characterized by expression of the CD25 component of the IL-2 receptor.

Denileukin diftitox has been associated with a variety of acute infusion-related reactions. These include cutaneous reactions such as pruritis or flushing and systemic reactions such as dyspnea, chest pain or tightness, and back pain. Infusion-related symptoms typically occurred during or within 24 h of the infusion of the drug. Dyspnea occurred in 20% of patients in the pivotal phase III trial, back pain in 17%, hypotension in 17%, chest pain or tightness in 13%, pruritis in 13%, and flushing occurred in 13% of patients [55]. These reactions typically resolve after temporarily disrupting the infusion or after administration of antihistamines and/or corticosteroids [55]. Fever, chills, myalgias, arthralgias, headache, diarrhea, anorexia, and asthenia are also commonly associated with treatment with denileukin diftitox. Flu-like symptoms may be managed with antipyretics, antiemetics, and/or antidiarrheal agents. Vascular leak syndrome (VLS) occurs in up to 27% of patients receiving the drug [56]. VLS is characterized by edema, hypoalbuminemia (≤2.8 g/dL), and/or hypotension occurring within the first 14 days following treatment [55]. Steroid premedication prior to administration of denileukin diftitox with agents such as prednisone or dexamethasone can significantly reduce the risk of VLS [56].

Denileukin diftitox has been associated with visual changes in small numbers of patients [57, 58]. Dang et al. reported that two of 38 patients who received denileukin diftitox for relapsed/refractory B-cell non-Hodgkin lymphoma experienced visual changes felt to be associated with the drug [57]. The first patient experienced transient decreased visual acuity after receiving two cycles; however, the second patient experienced permanent loss of visual acuity after eight cycles. The exact mechanism is unclear. However, a potential link between altered T-cell immunity and autoimmune retinitis may exist as demonstrated in animal models [59].

Bexarotene

Bexarotene (Targretin®) is an oral synthetic retinoid that is selective for the retinoid X receptor (RXR). In 1999, bexarotene became the only retinoid to gain FDA approval for use in CTCL. Bexarotene leads to dose-dependent adverse effects including hypertriglyceridemia (82%), hypercholesterolemia (30%), central hypothyroidism (29%), and leukopenia (11%) [60].

Successful management of hypertriglyceridemia can be achieved through the use of lipid lowering agents, and there is evidence that response rates of bexarotene are higher when triglycerides are managed appropriately [61]. Fenofibrate has been shown to be effective as a triglyceride-lowering agent, either alone or in combination with a statin such as atorvastatin [61]. Patients should also be counseled on the adoption of a low-fat diet. Because of a paradoxical association with increased bexarotene levels, Gemfibrozil should not be used for the treatment of bexarotene-induced hypertriglyceridemia. In addition, Gemfibrozil has been associated with increased triglyceride levels and increased risk for pancreatitis [61]. Prescribing a lower starting dose of bexarotene (75–150 mg), monitoring weekly fasting triglyceride levels, and starting lipid-lowering agents 1 week prior to beginning therapy with bexarotene has been recommended as a useful therapeutic strategy [62].

Central hypothyroidism occurs in an estimated 29% of those receiving oral bexarotene therapy for CTCL [60]. Bexarotene has been shown to suppress thyrotropin secretion which results in reversible central hypothyroidism manifest by low thyroid stimulating hormone (TSH) and low T_4 levels [63]. TSH levels will remain low while the patient is taking bexarotene due to the drug's suppression of thyrotropin [61]. In view of its effect on thyroid hormonal axis, checking TSH and T_4 levels prior to beginning therapy with bexarotene followed by frequent monitoring of only free T_4 levels once bexarotene has been initiated would be recommended. Thyroid hormone supplementation should be administered and can improve T_4 levels as well as symptoms of cold intolerance and fatigue [61, 63].

Histone Deacetylase Inhibitors

Vorinostat (Zolinza®; Merck, Whitehouse Station, NJ) is an oral histone deacetylase (HDAC) inhibitor which was FDA approved for the treatment of relapsed or refractory CTCL in October 2006. In the pivotal phase IIB multicenter registration trial, the most common adverse events associated with the drug were gastrointestinal or constitutional symptoms, hematologic abnormalities (thrombocytopenia [21.6%]; anemia [12.2%]), or taste disturbances [64]. While most drug-related adverse events were grade 2 or lower, the grade 3 or higher adverse events included fatigue (5%), thromboembolic events (5%), thrombocytopenia (5%), and nausea (4%) [64]. Because of the risk for thromboembolic events, vorinostat should be used with caution in patients with a history of deep venous thrombosis or pulmonary embolism. Preclinical studies have raised concerns about the possibility of QTc prolongation as a class effect of the HDAC inhibitors. Electrocardiogram changes, including ST-T wave changes and QTc prolongation, were observed in the pivotal vorinostat trial; however, these electrocardiogram findings were clinically insignificant [64].

Romidepsin (Istotax®, Gloucester Pharmaceuticals, Cambridge, MA) is a novel HDAC inhibitor that, in early studies, has been shown to have activity in refractory CTCL and peripheral T-cell lymphoma [65–67]. Romidepsin was granted FDA approval for use in CTCL in November 2009. In a phase II multi-institutional trial of romidepsin, the drug was initially administered as a 4 h infusion at 18 mg/m^2 on days 1 and 5 of a 21-day cycle [66]. This schedule was altered, by amendment to the trial, to a more tolerable dosing schedule of 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. In a total of 71 patients, the most common non-hematologic adverse events included nausea (52%), fatigue (41%), vomiting (20%), and anorexia (21%). The most common hematological adverse events included thrombocytopenia (37%), anemia (37%), neutropenia (37%), and lymphopenia (21%). Grade 1 hyperuricemia occurred in 11% of patients, and grade 4 hyperuricemia occurred in 4%. Other electrolyte abnormalities (any grade) that were seen included hypocalcemia in 42%, hypomagnesemia in 15%, and hypophosphatemia in 8%.

The evaluation of potential cardiac adverse effects was also systematically evaluated in the recently published phase II trial of romidepsin [66, 68]. In the 71 patients in the trial, 20 patients had cardiac events [66]. These included QTc prolongation in 16 patients, atrial fibrillation in three,

supraventricular and ventricular ectopy in three, sinus bradycardia in two, and junctional rhythm in one patient. Piekarz and colleagues noted that eight of the 16 patients who experienced QTc prolongation were noted to have had preexisting abnormal QTc intervals of greater than 450 ms. In addition, there may be some effect on the QTc interval of antiemetics and concomitant medications which may be metabolized through CYP3A4 [66, 69]. The authors caution the use of drugs which prolong the QTc interval or inhibit the CYP3A4 enzyme concurrent with the use of romidepsin. In addition, electrolyte replacement and routine monitoring of serum potassium and magnesium levels is recommended [66, 68].

Pralatrexate

Pralatrexate (Folotyn®; Allos Therapeutics, Inc., Westminster, CO), structurally similar to methotrexate, is a drug in the 10-deazaaminopterin class of folate analogs. It has recently been shown to have activity in chemotherapy-refractory T-cell lymphomas [70, 71], and it gained FDA approval in September 2009 for use in relapsed or refractory peripheral T-cell lymphoma. The major toxicities of pralatrexate were dose-dependent and consisted of stomatitis and myelosuppression (grade 3 or 4 leukopenia, lymphopenia, and thrombocytopenia) [71]. Vitamin supplementation with folic acid (5 mg orally beginning 3 days prior to initiation of therapy) and vitamin B12 (1,000 μg orally daily or 100 μg intramuscularly every 8–9 weeks) reduces the risk of both stomatitis and myelosuppression [71].

Other Agents

Gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, IN) is a nucleoside analog that inhibits its DNA synthesis. It has activity in a wide variety of solid tumors as well as in hematologic malignancies [72]. Gemcitabine has been studied in relapsed or refractory peripheral T-cell lymphoma and CTCL [73–76]. The most common adverse effects of this drug include myelosuppression, elevation of hepatic transaminases, hyperpigmentation [76]. There have been rare cases of hemolytic-uremic syndrome during therapy with gemcitabine [76].

Horwitz et al. reported results from their phase I/IIA study evaluating the combination of pralatrexate and gemcitabine in patients with relapsed or refractory lymphoid malignancies [77]. Preliminary results revealed that when these drugs were used more frequently than once every 2 weeks, the grade 3 and 4 hematologic toxicity rendered the regimen very poorly tolerated by the heavily pretreated patients in the study. Grade 3 or 4 neutropenia and thrombocytopenia were experienced by 9 of 20 patients (45%), and grade 3 or 4 anemia was experienced by 8 of 20 patients (40%).

Pentostatin, an adenosine deaminase inhibitor that is selectively toxic to lymphocytes, has been shown to have activity in T-cell malignancies [78–81]. The major adverse effects of pentostatin include hematologic toxicity (including lymphopenia), renal insufficiency, nausea, and conjunctivitis [82]. Pentostatin-associated lymphopenia is likely due to selective depletion of CD26+ T-lymphocytes as demonstrated by Dang et al. [79]. CD26+ is a marker of activated T-lymphocytes, and their depletion—and subsequent suppression of the immune system—may explain the increased susceptibility to opportunistic infections in patients receiving pentostatin [79]. Cardiac toxicity has also been observed after pentostatin use. In patients with predisposing conditions—such as coronary artery disease, congestive heart failure, and hypertension—an association with angina, myocardial infarction, arrhythmias, and heart failure has been identified [83]. The risk of nephrotoxicity is dose-dependent, and renal toxicity is more likely to occur at doses higher than 4 mg/m^2/week [81, 84, 85]. Because of the risk for renal and cardiac toxicity, one should consider optimizing medical management of any preexisting cardiac disease, avoiding fluid overload or dehydration, and reducing the dose of pentostatin in those with impaired renal function [83].

Alemtuzumab (Campath®; Genzyme Corporation, Cambridge, MA/Berlex Oncology, Wayne, NJ) is a monoclonal antibody which

targets CD52, an antigen expressed on most B and T lymphocytes. Approved for use in B-cell chronic lymphocytic lymphoma (CLL), alemtuzumab has also demonstrated activity in advanced CTCL and relapsed or refractory peripheral T-cell lymphoma [86, 87]. In clinical trials, patients have had a high risk of infectious complications, likely due to a combination of factors including underlying lymphoid malignancy, exposure to prior therapies, and possibly disease refractoriness [88]. Alemtuzumab, because of the prolonged depression of B and T lymphocytes, increases this risk for significant infectious complications, including reactivation of cytomegalovirus (CMV) and opportunistic infections. CMV reactivation may occur in 15–25% of patients who receive alemtuzumab [88]. It is recommended that patients receive prophylaxis for *Pneumocystis pneumonia* (PCP) and herpes virus infections, and these prophylactic anti-infective agents should be continued for at least 2 months after completing therapy [88].

In addition to the infectious complications resulting from immune suppression, alemtuzumab is associated with infusion-related toxicity and myelosuppression. Fever, rigors, rash, nausea and vomiting, and hypotension may occur with intravenous administration. Administration of premedications, such as acetaminophen and antihistamines, and administration of prophylactic steroids may reduce the risk of these infusion-related side effects [88, 89]. While the approved dosing of alemtuzumab is intravenous, subcutaneous administration has been shown to be feasible, effective, and associated with less risk of infusion-related toxicity in treatment of chronic lymphocytic leukemia [90]. Subcutaneous administration is associated with transient first-dose skin reactions (erythema and edema), and premedications can alleviate the risk of this reaction [90]. Patients may experience transient mild cytopenias including delayed neutropenia or, less commonly, thrombocytopenia [87].

Bortezomib (Velcade®; Millenium Pharmaceuticals, Cambridge, MA) is a proteasome inhibitor which is FDA-approved for use in multiple myeloma and in mantle cell lymphoma. A phase II trial in relapsed or refractory CTCL confirmed that bortezomib has activity in both in CTCL and in peripheral T-cell lymphoma with skin involvement [91]. In the small phase II trial, there was no grade 4 toxicity; however, grade 3 toxicities included neutropenia, thrombocytopenia, and peripheral neuropathy [91]. These toxicities are consistent with those experienced when using bortezomib in multiple myeloma and mantle cell lymphoma. Dose modifications are recommended (per package insert) in the event of neutropenia, thrombocytopenia, neuropathic pain, or peripheral neuropathy.

Pegylated liposomal doxorubicin (Doxil; Ortho Biotech Products LP, Bridgewater, NJ) is an anthracycline, doxorubicin, which has been formulated in such a way that allows for longer half-life, reduced toxicity, and improved efficacy [92, 93]. In addition to its activity in solid tumors, such as ovarian cancer, and multiple myeloma, this agent has been shown to have activity in CTCL [94, 95]. The dose-limiting toxicity of pegylated liposomal doxorubicin is mucositis, however, mucositis typically occurs at very high doses (70 mg/m^2) [93]. Palmar plantar erythroderma (PPE), also known as hand-foot syndrome, is a more commonly experienced side effect. The risk of PPE is reduced when the dose is lowered or when the frequency of administration of doses is decreased. The cardiac toxicity of pegylated liposomal doxorubicin is dose dependent, but there is some controversy about the cumulative dose limit. The risk of cardiac effects is less than that of traditional doxorubicin [93].

Zanolimumab (HuMax-CD4®; Genmab, Copenhagen, Denmark) is a humanized monoclonal antibody which targets CD4, found in the T-cell receptor complex, thus blocking receptor-mediated T-cell signaling. Through this action, the drug induces antibody-dependent cell-mediated toxicity of neoplastic CD4+ T-lymphocytes. Zanolimumab was shown to have dose-dependent activity in refractory CTCL [96]. Side effects of this antibody include low-grade infections, primarily of skin and upper respiratory tract, and eczematous dermatitis [96].

The chimeric monoclonal antibody, SGN-30, targets cells that express CD30. CD30 is expressed in several hematologic malignancies, including

ALCL, the Reed Sternberg cell of Hodgkin lymphoma, and lesions of mycosis fungoides. It is also expressed in lymphomatoid papulosis. Preliminary data from phase II studies have indicated that SGN-30 has activity in refractory CD30+ ALCL as well as other CD30+ lymphoproliferative disorders [97, 98]. In these preliminary reports, SGN-30 appears to be well tolerated.

Siplizumab (MEDI-507) is a humanized monoclonal antibody directed at the CD2 receptor on T- and NK-cells. Preliminary results from two phase I trials in CD2-positive T-cell lymphoproliferative disorders showed encouraging results [99, 100]. Because of an association with the development of EBV-associated lymphoproliferative diseases (LPD), these trials were stopped early [101]. In 29 patients who received siplizumab for their T-cell malignancy, four patients (13.7%) developed an EBV-associated LPD [101]. The incidence of EBV-associated LPD occurred more in those patients treated on a weekly schedule (3 out of 7 patients, or 43%) than in those treated biweekly (1 out of 22 patients, or 4.5%). The patients who developed EBV-associated LPD were found to have significantly greater T-cell and NK-cell depletion.

In addition to the FDA-approved HDAC inhibitors, vorinostat and romidepsin, there are other HDAC inhibitors under investigation for use in T-cell lymphomas. Panobinostat (LBH589), an HDAC inhibitor available in an oral and an intravenous formulation, is being evaluated in a phase I dose-escalation study in patients with solid tumors and non-Hodgkin's lymphoma, and the oral HDAC inhibitor induced responses in the cohort of CTCL patients ($n=10$) [102]. Two patients achieved a complete response, four achieved a partial response, and one achieved stable disease. The maximum tolerated dose and schedule was found to be 20 mg orally on days 1, 3, and 5, weekly. In this small sample size of patients, the most common side effects were nausea, anorexia, fatigue, diarrhea, and transient neutropenia and thrombocytopenia; one patient experienced atrial fibrillation [102]. A phase II trial of panobinostat in refractory CTCL is currently ongoing and preliminary results confirm similar adverse events but also identified a small incidence of QTc prolongation [103]. Of 4,542 electrocardiograms, four were noted to have a prolongation of more than 60 ms from baseline, and two were found to have QTc intervals of more than 480 ms [103]. As with vorinostat and romidepsin, it is not clear that these QTc interval prolongations are clinically relevant [104].

Lenalidomide (Revlimid®; Celgene, Summit, NJ) is an immunomodulatory drug which is FDA-approved for the treatment of multiple myeloma and myelodysplastic syndrome. It is currently under investigation in CTCL [105] and in T-cell lymphomas other than CTCL [106]. In the CTCL phase II study, four of the nine evaluable patients experienced grade 1 fatigue, three experienced grade 2 lower extremity edema, and one patient each experienced grade 1 gastrointestinal symptoms and grade 2 anemia [105]. Hematologic toxicity was the primary toxicity reported in the recent phase II trial using lenalidomide in other T-cell lymphomas. Out of 23 evaluable patients, grade 4 thrombocytopenia occurred in 33% and grade 3 neutropenia occurred in almost 21% [106]. Febrile neutropenia and pain were each reported in 16.7% of the 23 patients.

An inhibitor of purine nucleoside phosphorylase (PNP), forodesine leads to intracellular accumulation of deoxyguanosine triphosphate resulting in apoptosis. Oral forodesine has shown activity in refractory CTCL, and the optimal dose has been determined to be 80 mg/m^2 daily [107]. Of 56 patients treated on the phase I/II dose escalation trial, grade 3 or higher adverse which occurred in two patients each included diarrhea, rash, cellulitis, and acute renal failure [108]. Occurring in one patient each were grade 3 vertigo, edema, and pneumonia. Lymphopenia (grade 3 or higher) occurred in 71% of patients, and there was one episode each of neutropenia (grade 1) and anemia (grade 3) [108]. For nine patients who received forodesine for more than 12 months, the most common adverse events were nausea ($n=4$), fatigue ($n=2$), peripheral edema ($n=2$), dyspnea ($n=2$), and urinary casts ($n=2$) [107]. None of the nine patients experienced hematologic or infection-related adverse events due to forodesine.

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