Cutaneous T-cell Lymphomas

Subjects: Others

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Although various anti-cutaneous T cell lymphoma (CTCL) therapies are available for clinical use, appropriate chemotherapy lines for the treatment of CTCLs have yet to be established. Therefore, to date, various clinical trials for the treatment of advanced CTCLs are ongoing. In this review, we evaluate the therapeutic options that are available in clinical practice, for treatment of early- and advanced-stage CTCLs (targeted therapies, histone deacetylase (HDAC) inhibitors, retinoids, interferons, cytotoxic drugs, etc.). We also examine clinical trials of novel regimens for the treatment of CTCLs.

CTCL topical formulation bexarotene targeted therapy interferon

1. Surface Molecular-targeted Therapy for Advanced CTCLs

Among surface molecular-targeted therapies, mogamulizumab, brentuximab vedotin, denileukin diftitox, alemtuzumab, and pembrolizumab are recommended by the 2020 NCCN guidelines for the treatment of primary cutaneous lymphomas [1] (Table 1).

Table 1. The efficacy of systemic formulations for treatment of CTCLs.

Protocol	ORR (%)	CR (%)	PR (%)	PFS	Most Common AEs (%)	Most Common SAEs (%)
Mogamulizumab	28			7.7 months	infusion reaction (32%)	pyrexia (4%)
Brentuximab vedotin	56.3				neuropathy (50%)	neuropathy (5%)
Denileukin diftitox	44	10	34	>2 years	fatigue (12%)	capillary leak syndrome (2%)
Pembrolizumab	37.5	8.3	29.2			

Alemtuzumab	51.1	17.9	33.3	3.4 months		severe infectious AEs (62%)
High-dose IFN-a2a	29	4	25			
IFN-a2a plus PUVA	80.6	74.6	6	32 months		
IFN-a2b with PUVA	93	73	20	>2 years		
IFN-g	60			>170 days	flu-like illness (100%)	
Bexarotene	45				hypertriglyceridemia	hyperlipidemia
Vorinostat	29.5			9.8 months	diarrhea (49%)	thrombocytopenia (5%)
Romidepsin	33.8	5.6	28.2	13.7 months	nausea (73.2%)	
Quisinostat	24			2.8–6.9 months	nausea, diarrhea (23%)	hypertension (11.5%)
Pralatrexate	44.8	3.4	41.4		mucositis (48%)	mucositis (17%)
Gemcitabine	75	21.8	53.1	10 months		
Pegylated liposomal doxorubicin	56	20	36	5 months		

PFS: progress free survival, SAE: severe adverse event

2. Immunomodulatory Reagents: Interferon (IFN), Bexarotene, Etoposide

Immunomodulatory reagents have been used classically for the treatment of CTCLs. Among these reagents, IFN and bexarotene recently have been investigated for their immunomodulatory effects on the CTCL tumor microenvironment [2][3][4]. These reports suggest the possible utility of combination therapies for CTCL, such as IFN-α2a in combination with psoralen with ultraviolet light A (PUVA), low-dose methotrexate, or retinoid [5][6][7], or bexarotene plus phototherapy [8][9]. Preclinical findings suggest that more immunomodulatory reagent-based combination therapies will be established in the future.

3. HDAC Inhibitors (Vorinostat, Romidepsin, Quisinostat)

HDAC inhibition restores histone acetylation in CTCL cells to normal levels, thereby activating gene expression and leading to the induction of growth arrest, cellular differentiation, and apoptosis [10][11]. Indeed, various HDAC inhibitors have been investigated for the treatment of CTCL. Among these compounds, vorinostat has been approved by the FDA for the treatment of advanced CTCL. Initial clinical trial reports found an ORR of 29.5% for patients with CTCL at Stage IIB or higher [64]. Median time to progression was 9.8 months for responders at Stage IIB or higher. The most common drug-related AEs were diarrhea (49%), fatigue (46%), nausea (43%), and anorexia (26%), and the most common SAEs were fatigue (5%), pulmonary embolism (5%), thrombocytopenia (5%), and nausea (4%). Notably, in another clinical trial, the median PFS with vorinostat was 3.1 months (95% CI: 2.9–4.1 months) for relapsed CTCL, which is a value that is inferior to that obtained with mogamulizumab (HR 0.53; 95% CI 0.41–0.69; stratified log-rank $p < 0.0001$) [12].

Romidepsin is an another potent HDAC inhibitor that is isolated from the bacterium *Chromobacterium violaceum*; this compound has been approved by the FDA for the treatment of CTCL and peripheral T cell lymphoma (PTCL) [13]. The first phase II multi-institutional trial of romidepsin monotherapy for CTCL showed an ORR of 33.8% (95% CI: 23–46%) with four cases of CR (5.6%) and 20 cases of PR (28.2%), and the median DOR was 13.7 months. Safety profiles included nausea (73.2%), fatigue (57.7%), vomiting (26.8%), transient thrombocytopenia (56.3%), granulocytopenia (50.7%), anemia (52.1%), and leukopenia (42.3%).

Quisinostat is a second-generation pan-HDAC inhibitor with a broad spectrum of preclinical anti-tumor activity against various hematological malignancies, including CTCL [14]. Recently, the results of a phase II multicenter trial of oral quisinostat in 26 patients with previously treated MF or SS were reported [66]. The ORR was 24% as assessed by cases with >50% reduction of mSWAT score; the DOR in skin ranged from 2.8 to 6.9 months. The most common drug-related AEs were nausea, diarrhea (23%), asthenia (15%), hypertension (8%), thrombocytopenia (11%), and vomiting (11%) [15]. The incidence of SAEs was 11.5%, including single cases of

hypertension, lethargy, and pruritus. Overall, quisinostat appears to be better tolerated than first-generation HDAC inhibitors such as vorinostat or romidepsin.

4. Anti-Metabolic Drugs: Pralatrexate, Methotrexate (MTX)

Paralatrexate is an antineoplastic folate analog similar to MTX; both compounds exhibit high affinity for the reduced folate carrier type-1 oncoprotein [16][17][18]. Paralatrexate inhibits dihydrofolate reductase, thereby disrupting DNA synthesis and leading to the induction of cytotoxicity against CTCL cells [19]. In a preclinical study, paralatrexate showed superior activity against human lymphoma cells compared to MTX [20]. A phase I dose de-escalation study for relapsed or refractory CTCL suggested that the ORR of pralatrexate was 45% (13/29) (95% CI: 26.4–64.3%) with 1 case of CR and 12 of PR [21]. The most common AEs were mucositis (48%), fatigue (41%), nausea (31%), edema (28%), epistaxia (21%), pyrexia (21%), anorexia (21%), and skin toxicity (21%). The most common SAEs were mucositis (17%) and leukopenia (3%). More recently, Duvic et al. reported the results of a phase I/II open-label, multicenter clinical trial for pralatrexate (15 mg/m^2) plus bexarotene (150 mg/m^2) combination therapy for relapsed or refractory CTCL [22]. The ORR was 60% (18/31), including four cases with CR and 14 with PR; the DOR for CR patients was 9.0 to 28.3 months. The median PFS was 12.8 months [23]. The most common AEs with this combination therapy were stomatitis (65%), hypertriglyceridemia (56%), fatigue (44%), nausea (32%), neutropenia (32%), central hypothyroidism (24%), and anemia (24%) [24]. The most common SAEs were neutropenia (35%), hypertriglyceridemia (29%), and stomatitis (21%) [25] Overall, pralatrexate is effective for relapsed or refractory CTCL with acceptable toxicity, especially when administered in combination with bexarotene.

MTX is an analog of folic acid that has been used classically (since 1964) for the treatment of MF [26][27]. In addition, a retrospective study of low-dose MTX for the treatment of patients with MF has been conducted [28]. The ORR of low-dose MTX for MF was 30.4% (21/69), including seven cases with CR and 14 with PR [28]. Notably, most of the responding patients had early-stage (patch or plaque) MF, with the exception of one patient with tumor-stage disease [28]. In addition, the results of a multicenter observational study of MTX for the treatment of patients with MF found an ORR of 70.9% (56/79) [22]. Those authors concluded that the response of subjects with MF to MTX depended on the dose of MTX and the stage of MF [22]. Overall, low-dose MTX monotherapy is well-tolerated and effective, especially for MF, notably in early-stage disease.

5. Miscellaneous Therapies Preferred Systemic Therapies: Gemcitabine, Pegylated Liposomal Doxorubicin, and Extracorporeal Photopheresis (ECP)

As described above, the NCCN guidelines for primary cutaneous lymphomas suggest a systemic therapy option for the treatment of advanced MF/SS [1]. Among cytotoxic drugs for CTCL, gemcitabine and pegylated liposomal doxorubicin are recommended as SYST-CAT B together with brentuximab vedotin and pralatrexate [1]. Gemcitabine is a pyrimidine antimetabolite that has been used for the treatment of advanced CTCL. Two phase II studies have been reported. The first found an ORR of gemcitabine monotherapy of 75% (24/32) for CTCL

(including MF, peripheral T cell lymphoma, and SS), with seven cases of CR, and 73% (19/26) for MF with six cases of CR; the median PFS for CTCL was 10 months [29]. In the second report, the ORR of gemcitabine monotherapy was 68% (17/25) for CTCL, with three cases of CR, and the median PFS for CTCL was 4.1 months [30]. Pegylated liposomal doxorubicin, which is doxorubicin encapsulated in liposomes that leads to decreased cardiotoxicity and nephrotoxicity, is recommended for the treatment of CTCLs in the NCCN guideline as SYST-CAT B [1]. A prospective multicenter study found an ORR of pegylated liposomal doxorubicin for MF/SS of 56% (14/25), with five CR (20%), and a median PFS of 5 months [31]. Although CHOP is the standard regimen in patients with non-Hodgkin's lymphoma including CTCL [32], the DOR is limited compared to surface molecular-targeted therapy such as brentuximab vedotin [33]. Overall, these cytotoxic drugs could be other options for the treatment of CTCL, although the incident ratio of SAEs was high (36–40%) [31][32]. Etoposide, chlorambucil, cyclophosphamide, pentostatin, temozolomide, and bortezomib are also recommended in the NCCN guidelines as useful drugs under certain circumstances [1].

ECP is a leukapheresis-based therapy that exposes the isolated lymphocytes from peripheral blood to 8-methoxypsoralen and ultraviolet A radiation, and it has been used for the treatment of CTCL as SYST-CAT A[34]. The ORR of ECP for SS has been found to be 55.7% with a CR rate of 17.6% [35]. Notably, since ECP can be combined with other systemic therapies such as IFNs and bexarotene [36], ECP should be considered for the treatment of CTCL, although the availability of ECP might be limited.

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