bjh review

The changing therapeutic landscape, burden of disease, and unmet needs in patients with cutaneous T-cell lymphoma

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Summary

Cutaneous T-cell lymphomas (CTCLs) have a chronic, relapsing course, and the most common subtypes are mycosis fungoides and Sézary syndrome. The disease causes visible skin alterations and can also cause alopecia, pruritus and pain, all of which can impact patients' health-related quality of life (HRQoL). The goal of treatment is to reduce symptoms and prevent disease progression. However, treatment recommendations are often based on low levels of evidence due to the lack of well-designed randomised clinical trials and treatment guidelines, and approved drugs vary considerably across different countries and regions. Currently, available treatments rarely lead to durable remissions and eventually become less effective, meaning patients often require multiple therapy changes. Skin-directed therapies (SDTs) are first-line treatments for early-stage CTCL, whereas systemic therapies may be needed for early-stage disease that does not respond to SDT or for advanced-stage disease. However, patients can experience significant side-effects with these treatments or may be unable to tolerate them. Hence, there is an unmet need for effective therapies with good safety profiles for the treatment of early- and late-stage CTCL. Here, we review current treatment guidelines, investigational and approved treatments, the impact of CTCL on patients' HRQoL, and the treatment of pruritus.

Keywords: CTCL, mycosis fungoides, quality of life, Sézary syndrome, treatment strategies.

Current Management of CTCL

Cutaneous T-cell lymphomas (CTCLs) represent <4% of non-Hodgkin lymphomas in the USA[1] and present as erythema, papules, patches, plaques, nodules or tumours.[2] Several CTCL subtypes exist, but the most prevalent form is mycosis fungoides (MF),[1,3] followed by Sézary syndrome (SS),[4] which have estimated incidences of 0·3–0·9/100 000 and 0·1/1 000 000 respectively in Europe.[5,6] Patients with early-stage disease have a good prognosis, with 10-year overall survival (OS) rates of 50–90% depending on various prognostic factors. However, the prognosis for patients with advanced-stage disease is poorer, with 10-year OS rates of 15–53%[7,8] and a median OS of 2–5 years.[9] Diagnosis of MF and SS is based on multicompartmental assessment of disease in the skin (T), lymph nodes (N), visceral organs (M), and peripheral blood (B), referred to collectively as TNMB staging. Previously, blood involvement was not included in clinical staging of the disease,[10] but this was updated in 2007[11] following evidence that showed increased blood involvement adversely affects disease prognosis.[12,13]

Durable remission is uncommon in MF and SS, and patients tend to be treated with consecutive treatments until loss of response or intolerability. Periods of no therapy are common, particularly in the early stages, and are termed 'expectant' therapy or 'watch and wait'. In addition, symptom relief via methods such as anti-pruritic medication and emollients may be used. Allogeneic haematopoietic stem cell transplantation (allo-HSCT) may be indicated in a small number of eligible patients and is the only curative option.[8,14–16] Therefore, the goals of therapy are to improve or clear lesions and to control symptoms across all affected disease compartments (skin, blood, lymph nodes, and viscera), to minimise the risk of progression[17] and to avoid treatment-related toxicity.[18]

Earlier lines of therapy generally consist of skin-directed therapies (SDTs), radiotherapy, and biological response modifiers [National Comprehensive Cancer Network (NCCN) 2020].[8,19] Most treatments result in only partial responses[8] and most patients receive therapies until loss of response, meaning they move on to receive consecutive or combination treatments and often recycle their previous therapies. When systemic chemotherapy is required, single agents are preferred over combination chemotherapy such as the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) because of the short duration of

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responses and the higher toxicity profiles associated with combination chemotherapy (NCCN 2020).[19] Therapies with fewer side-effects and an absence of cumulative toxicity are often given in an ongoing or maintenance fashion[20] to improve and maintain disease control and quality of life (QoL) (NCCN 2020).[19] Systemic therapies are frequently combined with SDT.

Treatment recommendations are generally based on low levels of evidence due to the scarcity of well-designed randomised clinical trials[8,20–22] (NCCN 2020).[19] Few CTCL therapies are approved by the European Medicines Agency (EMA), with the majority having orphan status (Table I)[23–29]. In the latest treatment guidelines from the British Association of Dermatologists (BAD) and UK Cutaneous Lymphoma Group (UKCLG), clinical trials are included as second- and third-line treatment options for all disease stages except MF Stage IA/IIA, confirming a need for new therapies.[8]

The identification of specific CTCL biomarkers has allowed for the development of targeted therapies such as monoclonal antibodies, histone deacetylase inhibitors (HDACi), and proteasome inhibitors,[30] but there is still a lack of curative therapies.

Cutaneous T-cell lymphomas can also greatly impact patients' health-related QoL (HRQoL) through physical symptoms, such as pruritus and pain,[31,32] and non-physical factors, such as insomnia, anxiety and depression.[33] As CTCL is visible on the skin, patients experience relatively poor HRQoL,[34–36] even in the very early stages of disease.[34] Further, women with newly diagnosed MF or SS and those with alopecia have significantly impaired HRQoL.[37] Hence, it is important to consider the patient's HRQoL when selecting treatment, particularly in patients with late-stage MF or SS.[38] The effect of CTCL on patient QoL should however be considered during treatment option selection, particularly the effect of leaving early-stage disease untreated. Patients themselves may wish for early intervention even with a low chance of success.

In addition, there is a profound effect upon those family members who become caregivers to a person diagnosed with CTCL. Caregivers for those with advanced CTCL in particular can face extreme distress as the disease progresses, given the poor disease prognosis and lack of curative therapies.[39] This burden and its increase with time, is reflected in their own loss in QoL.[40]

The present review will describe the unmet needs, novel therapies (Table II)[23,27,41–59], and disease burden experienced by patients with CTCL.

Treatment guidelines

Various groups have published guidelines for MF and SS treatment, such as the International Society for Cutaneous Lymphoma (ISCL); the European Organisation for Research and Treatment of Cancer (EORTC); BAD and UKCLG; and the National Comprehensive Cancer Network (NCCN, USA-based; NCCN 2020).[8,19,20] In general, CTCL treatments are listed as first-, second- or third-line, and no preference is given for treatments within each line of therapy. SDTs tend to be recommended for early-stage disease, with biological response modifiers reserved for late-stage disease. Patients may be given several first-line treatments before they move to second-line therapies.

There is no contemporary, global consensus on treatment guidelines. In the NCCN guidelines, systemic therapies, such as brentuximab vedotin, are recommended as second-line therapy even for Stage IA patients with persistent skin disease, while the BAD recommends the treatment as second-line therapy from Stage IIB only. Regional guidelines mean that treatment can vary greatly between countries. The available treatments also differ (e.g. vorinostat is approved by the United States Food and Drug administration [FDA] but not by the EMA) and even the structure of guidelines; e.g. the EORTC divides therapies into first- and second-line treatments for each disease stage, while the BAD and UKCLG designate first-, second- and third-line treatments.[8,20] However, several first-line therapies are usually tried before moving on to second-line options. Although more drugs are licensed by the FDA than by the EMA, a large-scale, global study of patients with advanced MF or SS found no difference in survival rates between patients in the USA and in Europe [9,60].

Recommendations in updated treatment guidelines have also changed. For example, total skin electron beam therapy (TSEB) was previously recommended by the EORTC as a first-line treatment for early-stage disease, but is now

Table I. Current systemic therapies approved by the EMA for treatment of CTCL.

Drug	Year approved	Reference
Roferon-A	1996	Roferon-A Patient Information Leaflet[28]
Oral bexarotene	2001	Targretin EPAR Medicine Overview[29]
Topical mechlorethamine gel	2012 (Orphan Designation)	Ledaga EPAR Summary[25]
	2017 (Marketing Authorisation)	Ledaga Product Information[25]
Brentuximab vedotin	2012 (Orphan Designation)	Brentuximab vedotin Orphan Designation[24]
	2012 (Marketing Authorisation)	Adcetris Product Information[23]
Mogamulizumab	2018 (Orphan Designation)	Mogamulizumab Orphan Designation[26]
	2018 (Marketing Authorisation)	Poteligeo Product Information[27]

CTCL, cutaneous T-cell lymphoma; EMA, European Medicines Agency; EPAR, European public assessment report.

Table II. Novel therapies in ongoing clinical trials for early- and late-stage CTCL.

Disease stage	Name	Treatment type	Mechanism	Reference
Early	FLASH	Phototherapy	Synthetic hypericin in the form of a topical gel is used as a photosensitiser with fluorescent light therapy	NCT02448381 NIHR Innovation Observatory Evidence Briefing (2017)[53]
	E7777	Recombinant cytotoxic fusion protein	Diphtheria toxin fragments A and B are combined with human IL-2 to target the IL-2 receptor, which is overexpressed in CD25+ CTCL	NCT01871727
	Low-dose PUVA	Phototherapy	Low-dose PUVA used as maintenance therapy	Vieyra-Garcia *et al.* (2019)[58]
	Resiquimod	Skin-directed therapy	A toll-like agonist against TLR7 and TLR8, leading to an increase in IFN-γ and TNF-α	Rook *et al.* (2015)[56]
	Lenalidomide	Immunomodulatory drug	An analogue of thalidomide that induces Th1 cytokine production and NK cell and T-cell activation	Querfeld *et al.* (2014)[55]
	MNA-D	Microneedle array	Doxorubicin is delivered directly into patches and plaques via a dissolvable MNA	NCT02192021
	Pimecrolimus	Immunomodulatory topical cream	Inhibits calcineurin, which inhibits cytokine expressions and blocks T-cell activation	EudraCT Number: 2014-001377-14 Eichenfield and Beck (2003)[48]
Late	Brentuximab vedotin	Monoclonal antibody	Directed against CD30 and conjugated with auristatin E, a tubulin inhibitor, which causes apoptosis by disrupting microtubules within malignant cells	Adcetris Prescribing Information[41] Adcetris Product Information[23]
	Cobomarsen (MRG-106)	Oligonucleotide inhibitor	Inhibits microRNA-155, which is involved in the proliferation of malignant cells, and helps to induce apoptosis	T-cell Lymphoma Forum Industry Innovations miRagen MicroRNA Oral Presentation (2019)[57] NCT03713320
	Mogamulizumab	Monoclonal antibody	Directed against CCR4, which is overexpressed on malignant T cells, and defucosylated to improve ADCC	Poteligeo Prescribing Information[54] Poteligeo Product Information[27]
	Panobinostat	Pan-histone deacetylase inhibitor	Acts against all class I, II, and IV histone deacetylase enzymes	Atadja (2009)[43] Duvic *et al.* (2013)[47]
	Pembrolizumab	Monoclonal antibody	Targets programmed death-1 receptor	Khodadoust *et al.* (2020)[49]
	Pegylated liposomal doxorubicin	Chemotherapy	Pegylation of doxorubicin in liposomal form leads to a longer half-life with reduced toxicity	Alpdogan *et al.* (2019)[42] Dummer *et al.* (2012)[46]
	Alemtuzumab	Monoclonal antibody	Directed against CD52 and kills malignant cells through ADCC or non-complement-mediated killing	Lowenstein *et al.* (2006)[51] Bernengo *et al.* (2007)[44]
	Bortezomib	Proteasome inhibitor	Inhibits transcription factor NF-κB, leading to the suppression of TGF-β1 and IL-10, which induces apoptosis and may inhibit CTCL cell migration	Zinzani *et al.* (2007)[59] Chang *et al.* (2015)[45]
	Dimethyl fumarate	Immunomodulatory drug	Inhibits transcription factor NF-κB, which is used by cancer cells to block apoptosis	Kiessling *et al.* (2009)[50] Nicolay *et al.* (2016)[52]
	IPH4102 (alone or in combination with chemotherapy)	Monoclonal antibody	Directed against KIR3DL2 (immunoglobulin-like receptor), which is overexpressed in SS	NCT03902184
	TTI-621	Recombinant fusion protein	Binds to CD47 and prevents an inhibitory antiphagocytic (do not eat) signal to macrophages	NCT02890368

ADCC, antibody-dependent cellular cytotoxicity; CCR4, C-C chemokine receptor 4; CTCL, cutaneous T-cell lymphoma; IFN, interferon; IL, interleukin; KIR3DL2, killer cell immunoglobulin-like receptor, three Ig domains and long cytoplasmic tail 2; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NK cell, natural killer cell; PUVA, psoralen and ultraviolet A; SS, Sézary syndrome; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumour necrosis factor.

recommended as a second-line treatment. Additionally, monochemotherapy has changed from being a second-line treatment to a first-line treatment for Stage IIB MF.[20,61] For TSEB, these changes are most likely due to an increase in the assessed quality of evidence available for TSEB in the most recent guidelines. In the case of monochemotherapy, it is most likely due to considering evidence for poly- and monochemotherapy separately in the most recent guidelines; polychemotherapy is still considered as a second-line treatment. Allo-HSCT is recommended for advanced-stage disease in the updated 2017 EORTC guidelines,[20] whereas it was not recommended in the previous version.[61] While allo-HSCT is potentially curative,[15,16] there is still much work to be done in understanding the optimal conditioning regimens, the best moment to recommend HSCT, and how prior systemic therapies will affect the transplant outcome.[15,62] Furthermore, allo-HSCT is only available in limited, specialist centres, making it not easily accessible.

Early disease

Unmet needs

Patients with early-stage disease (Stage IA/IIA) have the best long-term survival prognosis,[7,8] with Stage IA patients having a prognosis similar to that of the age-matched general population.[63] However, 20–25% of patients with early-stage disease progress to more advanced disease.[7,64] Additionally, patients with early-stage disease can exhibit significant blood involvement,[65] which is generally associated with a poorer prognosis compared with patients without blood involvement.[66] Currently, the Cutaneous Lymphoma International Prognostic Index (CLIPi) identifies patients as low-, intermediate- and high-risk of progression,[7] but its predictive ability may be limited.[64]

Cutaneous T-cell lymphoma has a chronic, relapsing course and patients generally undergo multiple consecutive therapies, with the intent of clearing the skin disease, minimising recurrence, preserving patients' HRQoL and preventing disease progression.[36,67] First-line treatments for early-stage CTCL are skin-directed, including topical corticosteroids, nitrogen mustards, and topical retinoids, as well as phototherapy, photochemotherapy and radiotherapy.[8,20] Response rates to topical therapies in patients with early-stage disease range from 54% to 94% (topical corticosteroids: 82–94%, nitrogen mustards: 58·5–94%, topical retinoids: 54–80%), with complete response rates of 10–86% (topical corticosteroids: 25–63%, nitrogen mustards: 13·8–86%, topical retinoids: 10–60%);[68] however, side-effects may limit treatment tolerability.[68] Phototherapy can produce relatively high response rates (63–100%), but is associated with side-effects such as secondary cancers, and patients often relapse soon after therapy ends.[8,20] In addition, access to treatments can also be an issue. For example, nitrogen mustards are not currently available in the UK and Spain.

Therefore, there is still a clear need for more effective and tolerable therapies for early-stage patients, including those who do not respond adequately to SDTs.

Novel therapies for early-stage disease

Phase I and II trials. Phase I and II trials are summarised in Table III.[55,56,69]

Phase III trials

Fluorescent Light Activated Synthetic Hypericin (FLASH). The Fluorescent Light Activated Synthetic Hypericin (FLASH) study is an ongoing, multicentre, randomised, double-blind, placebo-controlled Phase III trial in patients with Stage IA/IIA MF (NCT02448381). Patients receive photodynamic therapy using a topical gel comprising synthetic hypericin or placebo ointment in combination with fluorescent light therapy.

Hypericin is a natural compound found in St John's wort (*Hypericum perforatum*). It contains a photosensitizer that can be excited at wavelengths within the visible spectrum, giving it an advantage over other photosensitizers that require ultraviolet light.[70] In the FLASH trial, the synthetic hypericin SGX301 (Soligenix, Inc., Princeton, NJ, USA) is used as an ointment that can be applied topically to skin lesions and that is more actively taken up by cancer cells than normal cells. After exposure to fluorescent light, reactive oxygen species develop, which kill the cancer cells. In early studies, 58% of patients with CTCL responded to SGX301 *versus* 8% of patients treated with placebo, with an acceptable safety profile.[71] SGX301 has received orphan drug designation in the European Union and in the USA.

SGX301 may provide a safer, more convenient alternative to photochemotherapy with psoralen plus ultraviolet A (PUVA), which has been associated with an increased risk of secondary skin cancers in patients exposed to high numbers of PUVA treatments.[8,72]

Denileukin diftitox. Denileukin diftitox is a recombinant cytotoxic fusion protein, combining human interleukin (IL)-2 with diphtheria toxin fragments A and B.[73] The drug targets cells expressing the IL-2 receptor (IL-2R), which is highly expressed in CD25-positive (+) CTCL.[74] In a placebo-controlled pivotal trial,[75] response rates in patients treated with two different doses of denileukin diftitox were 38–49%, including complete responses in 9–11% of cases, which was statistically significant compared with placebo.[76] Progression-free survival (PFS) was also significantly longer compared with the placebo group (794–971 days). In another open-label Phase III study, patients with MF and SS Stage IA–III achieved an overall response rate (ORR) of 30·6%.[77]

Denileukin diftitox was approved by the FDA under the trade name Ontak® (Seragen, Inc., San Diego, CA, USA)[75] in 1999 for patients with persistent or recurrent CD25+ CTCL, and was the first drug in its class approved to treat a human disease.[74] However, the drug was discontinued due to production issues.[78]

Table III. Summary of Phase I and II trials related to early-stage disease.

Drug	Details
Immunomodulatory drug	
Resiquimod	Immune response modifier with anti-viral and anti-tumour activity. Phase I results: 11 out 12 patients (CTCL, Stage IA/IIA) experienced significant improvement.[56] Phase II study (NCT03292406): expected completion March 2021.
Lenalidomide	Approved for use in patients with multiple myeloma, myelodysplastic syndromes, and various B-cell lymphomas.[69] Phase II results: 28% ORR, all PR, seen across all disease stages, including refractory patients; patients had received a median of six prior therapies.[55] Phase I and I/II studies: evaluating lenalidomide in combination with durvalumab (NCT03011814) and brentuximab vedotin (NCT03302728).
Pimecrolimus	Phase II study (EudraCT no. 2014-001377-14): for patients with MF Stage IA/IIA currently ongoing.
Chemotherapy	
MNA-D	Small adhesive-like patches (aMNA), which have dozens of very small microneedles loaded with extremely low doses of doxorubicin. Phase I study (NCT02192021): the safety and dose-finding phase is complete; the efficacy and safety phase expected completion date is December 2022.

CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; MNA, microneedle applicator; MNA-D, microneedle array-doxorubicin; ORR, overall response rate; PR, partial response.

E7777 is a new, improved formulation that was evaluated in a Phase I dose-finding study of patients with persistent and recurrent CTCL in Japan, in whom it showed anti-tumour activity.[73] Additionally, a Phase II study with the ORR as the primary objective was completed in April 2019 (NCT02676778), and a Phase III, multicentre, open-label, single-arm study assessing dose, efficacy and safety (NCT01871727) was completed in March 2020.

Low-dose PUVA. Psoralen plus ultraviolet A was used as maintenance therapy in patients with early-stage MF by 88% of respondents to an online survey of members of the ISCL conducted in 2004,[79] despite the recognised increase in incidence of squamous cell cancer and melanoma in patients receiving multiple courses of phototherapy. Additionally, respondents indicated a lack of consistency in the frequencies and durations of maintenance phototherapy.[79]

A clinical trial was conducted to investigate the benefits of using low-dose PUVA as a maintenance treatment in patients with MF (NCT01686594).[58] At the time of study initiation, the EORTC recommended against the use of PUVA for maintenance therapy due to a lack of evidence for efficacy and safety.[61] In the updated EORTC recommendations, published in 2017, the use of PUVA as maintenance therapy is acknowledged, although the guidelines state that there is still a lack of supportive evidence.[20]

In the low-dose PUVA maintenance trial, patients received PUVA during a 12–24-week induction phase.[58] Patients with complete responses were then randomised to either PUVA maintenance twice weekly for 9 months or to no maintenance; however, the trial closed early due to low accrual. The median disease-free remission period was 15 months in patients who received maintenance PUVA compared with 4 months in patients without maintenance. In biomarker assessments, high baseline levels of C-X-C motif chemokine ligand 9 (CXCL9), CXCL11, CXCL12, tumour necrosis factor ligand superfamily member 13 (TNFSF13), and CXCL13 were negatively associated with response to PUVA, while high baseline levels of TNF-related weak inducer of apoptosis (TWEAK, also known as TNFSF12) were positively associated and patients who achieved a complete response had high levels of TWEAK. Owing to the low accrual, this study is limited by the small sample size in the randomised group ($n = 19$), but it is the first prospective randomised trial evaluating the use of PUVA as maintenance therapy.

Advanced disease

Unmet needs

Patients with Stage IIB–IV disease have a very poor median OS, ranging from 3–5 years.[9] Although allo-HSCT is a curative treatment option for patients with CTCL, at least half of patients who receive this treatment relapse within 1 year,[15,62,80] and graft-*versus*-host disease (GvHD) can lead to severe morbidity and death.[81] Additionally, further investigation is needed into factors affecting outcomes after allo-HSCT, such as the optimal conditioning regimens as well as patient selection and the best time for transplantation during the disease course.[81]

There is also a great unmet need for more effective therapies to improve outcomes in this advanced-stage patient population. Immunotherapies are the preferred first-line therapy over chemotherapy,[8,20] (NCCN 2020)[19] a systematic review of 13 chemotherapy regimens in CTCL found a short median time to next therapy (TTNT) of only 3·9 months for mono- or polychemotherapy.[82] Additionally, a second review

found the relative risk of death for both mono- and poly-chemotherapy to be elevated compared with other lines of treatment.[60] Biomarker and genetic analyses have led to the development of several new targeted therapies.[30]

Novel therapies for late-stage disease

Phase I and II trials. Phase I and II trials are summarised in Table IV.[45–47,49,50,59,83–97]

Phase III trials. The current E7777 trial (NCT01871727), as mentioned previously, is open to patients with any stage of CTCL. A previous Phase III study using the old formulation, denileukin diftitox, included 15 (42%) patients with late-stage CTCL, of whom four (27%) achieved a response.[77]

For late-stage disease, systemic therapies are recommended.

Brentuximab vedotin. Brentuximab vedotin (Adcetris®, Takeda Pharmaceutical Co. Ltd., Tokyo, Japan) is an anti-CD30 monoclonal antibody conjugated with monomethyl auristatin E (MMAE), a cytotoxic drug that inhibits tubulin, leading to apoptosis through microtubule disruption (Adcetris Product Information).[23] It specifically targets CD30+ CTCL, which is present in ~30% of patients with CTCL.[98] In a multicentre, international, open-label, randomised, Phase III trial, patients were randomised to brentuximab vedotin or physician's choice (methotrexate or bexarotene, 64 patients in each treatment arm).[99] Patients must have had CD30+ MF or primary cutaneous anaplastic large-cell lymphoma (pcALCL) and have had received at least one prior therapy. Patients with additional diagnoses of SS or B2 blood involvement were excluded from the study. In total, 128 patients were in the intent-to-treat population: 97 patients with CD30+ MFand 31 with pcALCL. The primary end-point was an ORR of ≥4 months.

At a median follow-up of 22·9 months, the 4-month ORR was 56·3% in the brentuximab vedotin arm and 12·5% in the physician's choice arm. The PFS was significantly improved and symptom reduction was also seen.[99] The median TTNT was significantly greater for brentuximab vedotin-treated patients (14·2 months) compared with those receiving the physician's choice (5·6 months).[100] Peripheral neuropathy was highly prevalent in the brentuximab vedotin-treated patients compared with physician's choice-treated patients (44/66 and four of 62 respectively).[99] Based on these data, brentuximab vedotin was approved by the FDA in 2017 for the treatment of CD30+ MF and pcALCL following more than one prior systemic therapy (Adcetris Prescribing Information)[41] and by the EMA in 2018 for CD30+ CTCL (not including patients with SS) following more than one prior systemic therapy (Adcetris Product Information),[23] but it can only be administered for a maximum of 16 infusions. Early reports of real-world data of brentuximab vedotin have shown similar results in CD30+ CTCL.[101]

Brentuximab vedotin is also being evaluated in combination with lenalidomide in patients with relapsed/refractory CTCL regardless of CD30 expression status (NCT03302728) and in patients with Stage IB–IVB CTCL (NCT03409432).

Mogamulizumab. Mogamulizumab (Poteligeo®, Kyowa Kirin, Inc., Tokyo, Japan) is a defucosylated, humanised, monoclonal antibody targeting C-C chemokine receptor 4 (CCR4), which is thought to play a critical role in the migration of malignant T cells to the skin and is overexpressed in CTCL at all disease stages.[102] Defucosylation improves the antibody-dependent cellular cytotoxicity (ADCC) of the drug.[102,103] Mogamulizumab has demonstrated efficacy in patients with MF Stage IB–IVB and SS across disease compartments of the skin, blood, and lymph nodes.

Mogamulizumab was investigated in an international, open-label, randomised controlled Phase III trial for relapsed/refractory MF or SS. This study was the largest randomised study of systemic therapy in CTCL and the first to use PFS as a primary end-point, in line with international consensus guidelines.[11,104] In total, 372 patients with relapsed/refractory Stage IB–IVB MF or SS (204 and 168 patients respectively) who had failed at least one prior systemic therapy were randomised 1:1 to receive vorinostat or mogamulizumab. There were similar numbers of patients with MF and SS in each treatment arm: 105 patients with MF and 81 with SS for mogamulizumab; and 99 patients with MF and 87 SS for vorinostat. Vorinostat-treated patients who experienced intolerable toxicity or who had confirmed disease progression following at least two treatment cycles could crossover to mogamulizumab treatment.

The PFS, based on global composite scores of response in each disease compartment (i.e. skin, blood, lymph nodes, and viscera), was significantly longer with mogamulizumab (7·7 months) compared with vorinostat (3·1 months).[104] The ORR in skin, blood, and lymph node compartments was improved for 42%, 68%, and 17% of mogamulizumab-treated patients and 16%, 19%, and 4% of vorinostat-trested patients respectively. The ORR was improved overall for 28% of patients treated with mogamulizumab compared with 5% of the patients treated with vorinostat.[104] The TTNT was significantly prolonged for the mogamulizumab-treated patients compared with the vorinostat-treated patients (11 and 3·5 months respectively).[105] Between the mogamulizumab and vorinostat treatment discontinuation due to adverse events was similar (21·7% and 23·7% respectively), and there were also similar rates of drug-related serious treatment-emergent adverse events (19·6% and 16·7% respectively).[106]

Mogamulizumab was approved by the Japanese Pharmaceuticals and Medical Devices Agency (PDMA) in 2018 for relapsed/refractory CTCL,[107] by the FDA in 2018 for adult patients with relapsed/refractory MF or SS after at least one prior systemic therapy (Poteligeo Prescribing Information),[54] and by the EMA in 2018 for adult patients with MF or SS who had received at least one prior systemic therapy (Poteligeo Product Information).[102,27]

Table IV. Summary of phase I and II trials related to late-stage disease.

Drug	Details
HDACi	
Panobinostat	Approved in 2015 by the FDA for multiple myeloma.
	Phase II study results (NCT00425555): patients were stratified by previous bexarotene treatment. ORR was 17·3% for all patients, 15·2% for patients previously treated with bexarotene, and 20·0% for bexarotene-naïve patients. Median DOR was 5·6 months in patients previously treated with bexarotene, and had not been reached at the time of publication in the bexarotene-naïve group.[47] Median PFS was 4·2 and 3·7 months for patients with and without previous bexarotene exposure respectively.[47]
	Preclinical data suggested that panobinostat may be useful in treating CTCL patients whose disease is resistant to vorinostat through downregulation of STAT protein activity.[90]
Resminostat	Previously tested in Phase I or II studies in patients with hepatocellular carcinoma, Hodgkin lymphoma, biliary tract and pancreatic cancer, and non-small cell lung cancer.[86,92,93,95]
	Phase II study (NCT02953301): assessing the ability of resminostat as a maintenance treatment for patients with advanced-stage MF or SS who achieved disease control with another systemic therapy. Estimated completion date December 2021.
Humanised monoclonal antibody	
Pembrolizumab (anti-PD1)	Targets PD-1 receptor.
	Phase II study results: patients had received a median of ≥4 prior systemic therapies. ORR was 38%, with two patients achieving CR and seven achieving PR. Of the nine responders, all had ongoing responses at last follow-up. Median DOR had not been reached at the time of publication, with a median response follow-up time of 58 weeks.[49]
	Ongoing interventional trials include a Phase II study evaluating pembrolizumab the radiation therapy in MF and SS (NCT03385226); a Phase I study evaluating pembrolizumab with total skin electron beam radiation therapy in MF and SS (NCT03617224); a Phase I dose-finding study of pembrolizumab in combination with pralatrexate, decitabine, or both drugs (NCT03240211); and a Phase II study of pembrolizumab combined with romidepsin in patients with relapsed/refractory MF (NCT03278782).
Tislelizumab (anti-PD1)	Phase II study (NCT03493451): estimated completion date June 2020.
Atezolizumab (anti-PD1)	Phase II study (NCT03357224): estimated completion date June 2025.
Durvalumab (anti-PD1)	Phase I/II study (NCT03011814): estimated completion date June 2023.
Alemtuzumab (anti-CD52)	Phase II study results: safety and efficacy of alemtuzumab was evaluated in 22 patients with advanced, pretreated MF and SS in a single-arm Phase II trial.[87] Objective responses were seen in 55% of patients, with a CR rate of 32% and PR rate of 23%. The treatment appeared to be particularly effective for patients with SS, with six of seven experiencing complete clearance of Sézary cells. In patients with lymph node involvement, six of 11 achieved CR. Patients with erythroderma also responded better than those with plaques or tumours (ORR: 69% and 40%; CR: 38% and 30% respectively).
AFM13 (anti-CD30, anti-CD16A)	Phase Ia/IIb study (NCT03192202): estimated completion date August 2020.
	Phase II study (NCT04101331): estimated completion date February 2023.
IPH4102 (anti-KIR3DL2)	KIR3DL2 is expressed predominantly in SS.[84]
	Phase II study (NCT03902184): evaluate IPH4102 alone or in combination with chemotherapy in patients with relapsed/refractory MF/SS.
Chemotherapy	
PLD	Showed efficacy as a monotherapy in patients with relapsed/refractory CTCL.[88,89,97]
	Phase II study results: 20 patients (40·8%) achieved an objective response and three achieved CR. Patients with Stage IVA/B disease had lower response rates than those with Stage IIB (22% vs. 52%). Median DOR was 6 months and 80% of patients had a substantial improvement in cutaneous lymphoma manifestations.[46]
Romidepsin	Approved by the FDA for the treatment of patients with CTCL who have received ≥1 systemic therapy.
	Phase I study (NCT02512497): investigating the use of romidepsin in combination with fludarabine and busulfan, both before and after allogeneic HSCT, as a maintenance therapy to help to control lymphoma (including CTCL) or leukaemia, as well as to determine the optimal dose and safety of the treatment (NCT02512497). Estimated completion date December 2020.

Lacutamab. Another monoclonal antibody currently under investigation is IPH4102 (Lacutamab, Innate Pharma, Marseille, France),[108] which targets the cell surface protein killer cell immunoglobulin (Ig)-like receptor, three Ig domains and long cytoplasmic tail 2 (KIR3DL2) and, upon binding induces apoptosis of the cell via ADCC and antibody-

Table IV. (*Continued*)

Drug	Details
Proteasome inhibitor	
Bortezomib	Approved by the FDA for treatment of multiple myeloma and mantle cell lymphoma. It leads to apoptosis and may also inhibit CTCL migration by suppressing TGF-β1 and IL-10 through NF-κB inhibition.[45]
	Phase II study results: 15 patients with relapsed/refractory CTCL or peripheral T-cell lymphoma.[59] ORR was 70% in patients with MF and one patient achieved CR.
	Phase II study (NCT03487133): investigation in combination with dexamethasone in patients with relapsed/refractory CTCL. Estimated completion date December 2023.
Immunomodulatory drug	
DMF	Currently approved for multiple sclerosis (Tecfidera Product Information)[94] and plaque psoriasis (Skilarence Product Information).[91]
	Inhibitor of transcription factor NF-κB, which appears to block apoptosis in cancer cells.[83,85,96] Inhibition of NF-κB-induced apoptosis in malignant cells from patients with SS, while leaving healthy T cells unaffected.[50] Inhibition of NF-κB led to downregulation of FHC in malignant cells, which in turn lead to a rise in free cytosolic iron and ultimately cell death through reactive oxygen species. Downregulation of FHC was not seen in healthy T cells.
	Phase IIa study (NCT02546440): estimated completion date September 2021.
TTI-621	Phase I study (NCT02890368): dose-escalation trial involving patients with relapsed/refractory solid tumours or MF. Estimated completion date December 2019.

CR, complete response; DMF, dimethyl fumarate; DOR, duration of response; FDA, USA Food and Drug Administration; FHC, ferritin heavy chain; HSCT, haematopoietic stem cell transplantation; KIR3DL2, killer cell immunoglobulin-like receptor, three Ig domains and long cytoplasmic tail 2; MF, mycosis fungoides; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ORR, overall response rate; PD-1, programmed death-1; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response; SS, Sézary syndrome; STAT, signal transducer and activator of transcription.

dependent cellular phagocytosis.[109] This protein is overexpressed in T-cell lymphomas, including in >85% of patients with SS. In a Phase I trial, 43% (15/35) of patients with SS had a confirmed global overall response.[84] A Phase II trial (TELLOMAK) is ongoing (NCT03902184).

Vorinostat. The HDACi vorinostat (Zolinza®, Merck & Co., Inc., Whitehouse Station, NJ, USA) is also approved by the FDA for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease or following two systemic therapies. In a Phase II trial in patients with MF or SS refractory to or intolerant of prior therapies, the response rate was 24% by modified severity weighted assessment tool (mSWAT), with a median duration of response of 15 weeks.[110] In a Phase IIB trial in patients with MF and SS Stage ≥IB with progressive, persistent, or recurrent disease after two prior systemic therapies, the response rate was 29·7% and the median duration of response was ≥185 days.[11]

Romidepsin. Romidepsin (Istodax®, Celgene Corp., Summit, NJ, USA) is another HDACi that is FDA-approved for patients with CTCL and peripheral T-cell lymphoma (PTCL) following at least one prior systemic therapy. In a pivotal Phase II trial of patients with Stage IB–IVA CTCL who had received more than one prior systemic therapy, the ORR was 34% by mSWAT, with six patients achieving a complete response.[111] There are no approved HDACis in Europe for CTCL.

Effect of CTCL on HRQoL

Along with minimising symptoms and preventing progression, improving patients' HRQoL is an important therapy goal in CTCL. CTCL is a generally incurable disease that is characterised by visible skin alterations, such as patches, plaques and tumours, as well as by alopecia, pruritus and pain. The disease requires chronic treatment with a series of drugs, which can have significant side-effects and often lose effectiveness, meaning patients may require multiple therapy changes.

There are a variety of tools to assess patients' HRQoL that include domains for symptoms, function and emotions. Instruments commonly used in epidemiological and clinical studies of patients with CTCL are Skindex-29, a tool developed specifically for patients with skin disease, and generic tools such as the Functional Assessment of Cancer Therapy-General (FACT-G), 36-item Short Form Health Survey, EORTC Quality of Life Core Questionnaire (QLQ-C30), General Health Questionnaire and the Spitzer Quality of Life Index.[112]

Using the FACT-G questionnaire and the skin disease-specific Skindex-29 instrument, Demierre *et al.*[34] assessed HRQoL in 22 patients with CTCL. Their findings showed that patients with CTCL had low scores in physical, social/family, emotional, and functional well-being and symptoms.[34] In addition, patients with more advanced-stage disease had worse scores across all scales of both HRQoL

instruments, possibly reflecting more severe symptoms in advanced-stage CTCL and a greater risk of death.[34]

Wright *et al.*[36] also found lower HRQoL scores using Skindex-29 in patients with advanced-stage CTCL compared with patients with earlier-stage disease, with 88% of the participants reporting pruritus in the 4 weeks prior to completing the questionnaire; 46% reported experiencing pruritus 'often' or 'all the time'. However, advanced-stage CTCL is more than just a skin disease, and as such HRQoL may be affected in other ways that are not addressed by Skindex-29. In a survey conducted in 630 patients with CTCL, 88% of respondents indicated that they were bothered by itching, 83% by scaling, and 94% by skin redness. Some pain was reported by 41% of respondents and 13% reported 'quite a bit' to 'very much' pain.[35] Pruritus incidence and severity were associated with both early- and advanced-stage CTCL, measured using the visual analogue scale (VAS) for itch.[113] Further, CTCL impacted patients' abilities to meet the needs of their family, interfered with their job and led to missed work days, and significantly impacted their social interactions and sleep.[35] Fatigue was also reported by 66% of respondents and the disease led to patients feeling frustrated, angry and embarrassed, and worrying about the seriousness of their disease and possible death.

Jonak *et al.* (2019)[112] reviewed the Skindex-29 HRQoL assessments from three different epidemiological studies[34,36,114] and found reproducible results, with all studies showing that a majority of patients with CTCL worry about the seriousness of their illness and progression of the disease, and experience sleeping disorders and difficulties during their work, leisure time and social life.

Molloy *et al.* (2020)[37] used the Skindex-29 tool to examine the HRQoL of patients enrolled in the international, observational, MF/SS Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. They found that newly diagnosed women and those with alopecia experienced the worst HRQoL.[37] They suggested that a questionnaire specific to CTCL is necessary in order to better understand the HRQoL of these patients.

The need for a CTCL-specific tool

Due to the lack of effective curative therapies for CTCL, patients may live for many years experiencing the effects of the disease, with unpleasant symptoms such as pain, itching and functional deficit if the disease affects their hands or feet, and the emotional effect of living with long-term cancer.

In a 2018 two-arm clinical study comparing mogamulizumab with vorinostat, Skindex-29 and FACT-G were used to measure patient HRQoL as a secondary end-point.[104] Overall, both Skindex-29 and FACT-G showed that mogamulizumab was favoured over vorinostat.[115] However, when looking at the functioning domain, the differences between the results at treatment cycles seven and nine were significantly different for Skindex-29, but not for FACT-G. In the emotional domain, Skindex-29 showed vorinostat to improve on the baseline results, while FACT-G showed it to worsen. The discrepancies in results between these different tools emphasise the importance of using more disease-specific tools to measure HRQoL in patients with CTCL.

Molloy *et al.* (2020)[37] reported on 237 patients [60·3% male; median age 60 years (interquartile range 49–70)], of whom 179 had early-stage MF and 58 had advanced-stage MF/SS. HRQoL, as measured by Skindex-29, was worse in women, patients with SS, patients with late-stage MF and in those with raised lactate dehydrogenase, alopecia, higher mSWAT score and confluent erythema. Female sex and alopecia were also independent predictors of worse global HRQoL.

McCaffrey *et al.* (2019)[116] recently developed a CTCL-specific HRQoL tool (named MF/SS-CTCL QoL) in collaboration with the Cutaneous Lymphoma Foundation in order to fill this gap. Validation of the tool was performed through the PatientsLikeMe Open Research Exchange, by having patients (n = 126) complete the MF/SS-CTCL QoL questionnaire and also Skindex-29 as a comparator. A proportion of the patients (n = 66) then repeated MF/SS-CTL QoL after 5 days in order to assess test–retest reliability. However, the patient group that participated in the development of the tool predominantly had Stage I disease; therefore, data from advanced-stage patients are also required to improve the robustness of the tool.

The importance of pruritus control in improving patients' HRQoL

Pruritus affects a high proportion of patients and can affect other HRQoL factors by leading to difficulty falling asleep, depression,[34,35] and suicidal ideation (personal communication from P Ortiz-Romero, February 2020). Clinical studies of CTCL treatment showed that responders to the therapy had improved HRQoL, as well as improved skin and pruritus severity, suggesting that effective management and relief from pruritus impacts HRQoL. However, CTCL treatment guidelines focus on treating the disease itself and do not provide specific guidance on how to manage pruritus.[8,22]

Pathophysiology of pruritus in CTCL. The exact mechanism that causes pruritus in patients with CTCL is not fully understood, so pruritus is often managed by treating the disease rather than by using specific anti-itch treatments. The neuronal itch pathway can be stimulated by histamine, but itch in patients with CTCL is often unresponsive to treatment with anti-histamine agents or topical corticosteroids and may be due to 'histamine-independent' stimuli,[117] so other mediators must be considered.

There is evidence to suggest that itch in CTCL is related to inflammatory processes, with particular focus on IL-31.[118] Nattkemper *et al.* (2016)[118] found that IL-31 was significantly increased in the epidermis and lymphocytic infiltrate of

patients with CTCL, and that patients with moderate-to-severe itch had the highest levels of IL-31 in the skin where itch was evaluated using an itch-specific tool, the VAS-itch. IL-31 levels did not correlate with disease stage, implying that IL-31 is not directly involved in the pathogenesis of CTCL. However, a study in mice showed that repeated exposure to IL-31 led to long-lasting scratching,[119] implying that ongoing IL-31 exposure is needed for pruritus to develop. Altogether, this suggests that the ongoing, increased levels of IL-31 are a possible mechanism for pruritus in CTCL.

Pruritus therapies. Some therapies other than those that target the lymphoma itself have been effective in patients with CTCL.[117] For example, corticosteroids, both topical and oral formulations, can provide relief in some patients with CTCL.[120] Gabapentin, an anti-convulsant, and mirtazapine, an anti-depressant, have shown effectiveness in treating pruritus in patients with advanced-stage MF/SS.[121] In addition, aprepitant blocks the binding of substance P to the neurokinin-1 receptor and is approved for chemotherapy-induced nausea and vomiting. Substance P localises to mast cells, but has also been shown to induce itch in mast cell-deficient mice.[122] In a small case series of four patients with CTCL,[123] aprepitant improved pruritus, and a retrospective review involving 17 patients showed an ORR of 84%[124]; however, large-scale studies are needed to confirm these results. Naltrexone[125] and naloxone, both mu-opioid receptor antagonists, have also been used. Currently, a Phase III clinical trial is evaluating the effectiveness of naloxone lotion in patients with CTCL (NCT02811783), with results expected in 2021.

Conclusions

CTCL is characterised by visible skin alterations, such as patches, plaques and tumours, and also causes alopecia, pruritus and pain. Patient assessment requires a multicompartmental approach, including assessment of the level of blood involvement, and the same approach should be used when examining patient response to help determine the effect of treatment on disease stage.

The disease also requires chronic treatment with a series of therapies, which can have significant side-effects and often lose effectiveness, meaning patients may require multiple therapy changes. Patients with early-stage disease have a good prognosis; however, a subpopulation with refractory disease has limited treatment options when SDTs are no longer effective. Patients with advanced-stage disease have a poorer prognosis and therefore it is important to halt or slow disease progression as much as possible with improved duration of response and novel therapies. There is an unmet need for safe and effective therapies with good safety profiles for patients with both early- and late-stage CTCL. However, the recent development of targeted immunotherapies with good PFS, such as mogamulizumab and brentuximab vedotin, is changing the way that CTCL is now being managed, particularly for refractory patients. Another avenue to explore is the efficacy of maintenance therapy in order to improve the duration of response to existing therapies.

Allo-HSCT can offer a cure in some patients but comes at a price, including the likelihood of relapse, GvHD, or infection[15,62,80] and risk of death.[126] Further research is required into the optimal conditioning regimens and the best timing of HSCT following systemic therapy.

Cutaneous T-cell lymphoma also significantly impacts patients' HRQoL, which worsens as the disease advances. Patients experience itching and pain, as well as poor sleep, depression and anxiety. There are a variety of HRQoL measurement tools available, but the development of a CTCL-specific tool would more accurately reflect the effect of the disease on patients' lives. It is important that efforts be made to evaluate the patient perspective on their disease qualitatively and used to inform the development of any CTCL-specific HRQoL tool.

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Author contributions

All authors contributed equally to the planning, draft revisions and final approval of this manuscript.

Conflict of interest

Julia J. Scarisbrick receives honoraria from 4SC, Kyowa Kirin, Mallinckrodt, and Takeda; serves as a consultant/advisor for 4SC, Innate Pharma, Kyowa Kirin, Mallinckrodt, and Takeda; and receives research funding from Kyowa Kirin and Takeda. Martine Bagot has stock ownership in and patents/royalties with Innate Pharma, and serves as a consultant/advisor for Innate Pharma, Kyowa Kirin, and miRagen. Pablo L. Ortiz-Romero serves as a consultant/advisor for 4SC, Actelion, Innate, Kyowa Kirin, miRagen, Ricordati Rare Diseases, and Takeda; has patents/royalties with PLCG1 mutation; and receives travel funding from Almirall, Janssen, Leo Pharma, and Novartis.

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