New systemic treatment options in mycosis fungoides and Sézary syndrome

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Summary Cutaneous T cell lymphomas (CTCL) are a heterogeneous group of rare non-Hodgkin lymphomas. The most common type of CTCL is Mycosis fungoides (MF). Much less common but clinically and histopathologically related to MF is Sézary syndrome (SS). CTCL are incurable and associated with a reduced quality of life. While early stage MF has a good prognosis and is usually treated with skin directed therapies, advanced-stages require systemic therapies, including retinoids, interferon, cytotoxic chemotherapeutic drugs, low-dose methotrexate, histone deacetylase inhibitors and alemtuzumab. However, relapses are frequent and long-term remissions are achieved only in few cases, e.g. with allogeneic stem cell transplantation. In recent years, new therapeutic options have evolved by the approval of brentuximab vedotin and mogamulizumab. Both recently approved therapies demonstrated superiority with regard to overall response rate and progression free survival over traditional systemic therapies. Other promising treatments such as lacutamab and PD-1/L-1 inhibitors are in the pipeline, and more therapeutic agents are currently investigated in clinical trials.

Keywords Cutaneous T-cell lymphoma · Brentuximab vedotin · Mogamulizumab · Lacutamab · PD-1/L-1 inhibitors

Introduction

Cutaneous T cell lymphomas (CTCL) are a heterogeneous group of rare non-Hodgkin lymphomas characterized by infiltration of neoplastic T lymphocytes to the skin. The most common type of CTCL is mycosis fungoides (MF). Much less common but clinically and histopathologically related to MF is Sézary syndrome (SS) [1]. Reported age-adjusted incidence rates per 100,000 person-years in the United States (US) between 2005 and 2008 were 0.55 for MF and 0.01 for SS [2]. The clinical presentation and prognosis of MF vary widely and depend on clinical stage, ranging from limited skin involvement with patches and plaques to severe illness with ulcerated skin tumors, systemic involvement and death [3]. SS, which is more aggressive and clinically staged IVA-IVB [4], is defined by pruritic erythroderma, generalized lymphadenopathy and leukemic involvement [1]. CTCL are incurable and associated with a reduced quality of life [3, 5]. While early stage MF has a good prognosis and is usually treated with skin directed therapies, median survival ranges from 4.7 to 1.4 years in advanced stages of MF and SS (clinical stage IIB–IVB) [6]. Systemic therapies are then required, including retinoids, interferon alpha, cytotoxic chemotherapeutic drugs, low-dose methotrexate, histone deacetylase inhibitors (vorinostat, romidepsin, belinostat) and alemtuzumab [3]. However, relapses are frequent and long-term remissions are achieved only in few cases, e.g. with allogeneic stem cell transplantation [7]. In recent years new therapeutic options have evolved. These are discussed in detail in the following article.

Brentuximab vedotin

CD30, a cell surface receptor, is uniformly expressed in Hodgkin lymphoma (HL) and anaplastic large cell

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Table 1 Ongoing studies with PD-1/L-1 inhibitors in mycosis fungoides (MF)/(SS) Sézary syndrome as listed on ClinicalTrials.gov (accessed on March 30th 2020) [18]

NCT identifier	Official title	Phase	Recruitment status	Conditions	Interventions
NCT03240211	Pembrolizumab combined with Decitabine and Pralatrexate in PTCL and CTCL	Phase Ib	Recruiting	CTCL, PTCL	Pembrolizumab, Decitabine, Pralatrexate
NCT03385226	Pembrolizumab combined with radiotherapy in patients with relapsed, refractory, specified stages of cutaneous T-cell Lymphoma (CTCL) Mycosis Fungoides (MF)/Sézary Syndrome (SS) (PORT)	Phase II	Recruiting	MF/SS	Pembrolizumab + radiotherapy
NCT03617224	Pembrolizumab and Total Skin Electron Beam Radiotherapy in Mycosis Fungoides and Sézary Syndrome	Phase I	Recruiting	MF/SS	Pembrolizumab + TSEBT
NCT03063632	Pembrolizumab and Interferon Gamma-1b in treating patients with stage IB-IVB relapsed or refractory Mycosis Fungoides and Sézary Syndrome	Phase II	Active, not recruiting	MF/SS and others	Pembrolizumab + Interferon Gamma-1b
NCT03695471	Pembrolizumab in treating patients with stage IB-IV Mycosis Fungoides	Phase II	Recruiting	MF/SS	Pembrolizumab
NCT03598998	Pembrolizumab and Pralatrexate in treating patients with relapsed or refractory peripheral T-Cell Lymphomas	Phase I/II	Recruiting	MF and others	Pembrolizumab + Pralatrexate
NCT03278782	Pembrolizumab (MK-3475) in combination with Romidepsin	Phase I/II	Recruiting	MF and others	Pembrolizumab + Romidepsin
NCT02581631	Nivolumab in combination with Brentuximab Vedotin to treat Non-Hodgkin Lymphomas (CheckMate 436)	Phase I/II	Active, not recruiting	MF/SS and others	Nivolumab + BV
NCT02643303	In Situ Vaccination with Tremelimumab and iv Durvalumab plus PolyICLC in subjects with advanced, measurable, biopsy-accessible cancers	Phase I/II	Recruiting	CTCL and others	Durvalumab, Tremelimumab, Poly ICLC
NCT03011814	Durvalumab with or without Lenalidomide in treating patients with relapsed or refractory cutaneous or peripheral T cell lymphoma	Phase I/II	Recruiting	MF/SS and others	Durvalumab, Lenalidomide
NCT03357224	PARCT: Atezolizumab in relapsed/refractory cutaneous T Cell lymphoma (CTCL) (PARCT)	Phase II	Recruiting	CTCL	Atezolizumab
NCT03905135	Interleukin-15 (IL-15) in combination with Avelumab (Bavencio) in relapsed/refractory mature T-cell malignancies	Phase I	Recruiting	MF/SS and others	rhIL-15, Avelumab

lymphoma (ALCL) [8]. In CTCL CD30 expression is commonly seen in primary cutaneous anaplastic large-cell lymphoma (pc-ALCL) and lymphomatoid papulosis [1] and less frequently in MF and SS at various levels, ranging from 20–40% [9–11]. Brentuximab vedotin (BV) is an anti-CD30 antibody conjugated to the cytotoxic antitubulin agent monomethyl auristatin E (MMAE). The interaction between this complex and the CD30 ligand on lymphocytes leads to internalization into the cell where MMAE is released and causes an interruption of the microtubule network, inducing cell-cycle arrest and apoptosis. In addition, a small fraction of MMAE is released from CD30+ cells, killing neighboring cells in the tumor microenvironment in a CD30-independent manner [12]. In November 2017 the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved BV for patients with CD30+ CTCL that have received at least one systemic therapy [13, 14], based on the results of the ALCANZA study [15]. In this phase 3 trial, 97 patients with CD30+ MF and 31 patients with pc-ALCL pretreated with at least one systemic therapy or radiotherapy were randomly assigned to BV (intravenously 1.8 mg/kg every 3 weeks for up to 16 cycles) or to physician's choice (oral methotrexate 5–50 mg qw or oral bexarotene 300 mg/m² qd). CD30 expres-

sion of at least 10% of malignant cells or lymphoid infiltrate in skin biopsies was required. The primary endpoint was the percentage of patients achieving an overall response rate (ORR) persistent for at least 4 months (ORR4). This was reached in 50% of the MF patients in the BV group and in 10% in the physician's choice group. Responses to BV were seen in all clinical stages, albeit patients with SS were excluded from this study and approximately 3/4 of included patients had lower grade disease (stage IA–IIB). The progression free survival (PFS) was 15.9 months in the BV arm versus 3.5 months in the control arm. Side effects were similar to previous reports. The most common adverse event (AE) observed in the BV group was peripheral neuropathy (67%), which usually resolved after treatment discontinuation. Grade 3–4 AEs were reported in 41% of patients in the BV group and in 47% in the physician's choice group. One death was considered to be treatment related in the BV group. In sum, this study showed efficacy of BV in the treatment of refractory or relapsed CD30+ MF with CD30 expression levels of at least 10% [15]. Notably, in two smaller phase 2 trials the efficacy of BV was also demonstrated in CD30+ SS as well as in MF/SS with CD30 expression levels below 10% [16, 17], although response in patients with CD30 expression levels be-

low 5% was poor (17%) [16], suggesting that response to BV appears to be independent of CD30 expression only in patients with expression levels over 5–10%. Ongoing studies are examining BV in combination with other substances like nivolumab, romidepsin and lenalidomide in CTCL patients (Tables 1 and 2; [18]).

Mogamulizumab

C-C chemokine receptor type 4 (CCR4), a chemokine receptor important for T cell migration into the skin, is highly expressed on malignant T-cells and Tregs in MF and SS [19, 20]. Mogamulizumab is a CCR4-directed, defucosylated, monoclonal antibody that induces antibody dependent cellular cytotoxicity (ADCC) against CCR4+ malignant T cells and Tregs when binding to CCR4 [21]. In 2018 the FDA and the EMA approved mogamulizumab for relapsed or refractory MF and SS that has been pretreated with at least one systemic therapy [22, 23]. The basis of this approval was a phase 3 trial (MAVORIC) involving 372 patients with relapsed or refractory pretreated MF or SS [24]. Patients were stratified by CTCL subtype and clinical stage and were randomly assigned to mogamulizumab in the approved dose of 1.0 mg/kg intravenously once weekly for 4 weeks, followed by further cycles every other week, or to FDA approved vorinostat 400 mg daily. The primary end point was PFS, which was 7.7 months in the mogamulizumab group compared to 3.1 months in the vorinostat group. ORR to mogamulizumab was 28% versus 5% to vorinostat. In SS patients, the response rate to mogamulizumab was higher than in MF patients: 37% versus 21%. Stage dependent response to mogamulizumab was most significant in clinical stage IV: 36% versus 19% in stage IB or IIA. Compartment response was best in blood (68%), followed by skin (42%), lymph nodes (17%) and viscera (0%). The most common AEs of mogamulizumab were infusion related reactions, drug rash, diarrhea and fatigue. Grade 3–4 AEs were reported in 41% of patients, most frequently pyrexia and cellulitis. A total of 19% discontinued treatment due to toxicity. Two treatment-related deaths occurred, one case due to septicemia and another due to polymyositis. Overall, the safety profile was manageable and in accordance with previous reports. In brief, this study underscores the efficacy of mogamulizumab, particularly in SS and advanced stage MF [24]. However, patients with large cell transformation—a histological feature observed in 10–20% of MF/SS patients and associated with poor outcomes [10]—were excluded from this study. A phase 2 study evaluating mogamulizumab in combination with total skin electron beam therapy (TSEBT) in CTCL patients is expected to enroll in May 2020 (MOGAT, NCT04128072) [18].

Future perspectives

Lacutamab (IPH4102)

Lacutamab is a first-in-class monoclonal antibody targeting KIR3DL2, a cell surface protein that is frequently expressed by malignant T cells in CTCL, but not on normal CD4+ cells. Especially in SS, more than 85% of patients exhibit KIR3DL2 expression [25]. Lacutamab selectively depletes KIR3DL2+ cells through ADCC and phagocytosis [26]. In 2019, results of a phase 1 trial investigating the safety and activity of lacutamab in MF and SS were published [27]. In this study, 35 patients with SS, eight patients with MF and one patient with CTCL not otherwise specified were enrolled. Patients received at least two prior lines of treatment. The primary endpoint was the incidence of dose-limiting toxicities (grade 3 AEs or higher). Of note, no patient experienced such dose-limiting AEs. The most common grade 1–2 AEs were peripheral edema (27%) and fatigue (20%). The most common grade 3 toxicity was lymphopenia seen in 7% of patients. Only 9% of patients had to permanently discontinue treatment due to toxicity. ORR was 36.4% in all patients and specifically 43% in SS patients. In all patients, median DOR was 13.8 months and median PFS was 8.2 months, compared to 11.7 months in SS patients [28]. As a result, lacutamab received fast-track designation from the FDA for the treatment of patients with relapsed or refractory SS pretreated with at least two systemic therapies. Despite these promising results, lacutamab seems not to be effective in SS patients with large cell transformation as none of those patients showed a response. Currently, lacutamab is being investigated in a phase 2 study to evaluate the clinical activity and safety of lacutamab in MF, SS and other KIR3DL2 expressing T-cell lymphomas (TELOMAK, NCT03902184).

PD-1/L-1 inhibitors

It has been shown that PD-1 expression is high during early stage MF and that of PD-L1 in advanced stages with large cell transformation, likely contributing to immune evasion of malignant T cells [28]. PD-1/L-1 inhibitors prevent PD-1 from binding to its ligand, allowing T cell-mediated destruction of malignant lymphocytes [29]. Results of a phase 2 trial of pembrolizumab in the treatment of CTCL have been recently published [30]. Herein, 24 pretreated patients with advanced MF and SS received pembrolizumab 2 mg/kg every 3 weeks. The response rate was 56% in MF and 27% in SS (overall 38%). The median duration of response (DOR) was not reached after a median follow-up time of 58 weeks. Biomarker analysis showed no differences that might explain the discrepancy in response rates between MF and SS. The safety profile was consistent with other studies using PD-1 inhibitors. In 53% of SS patients, a transient wors-

Table 2 A selection of ongoing studies in mycosis fungoides (MF)/Sézary syndrome (SS) with other interesting substances not cited in the text, as listed on ClinicalTrials.gov (accessed on March 30th 2020) [18]

NCT identifier	Official title	Phase	Recruitment status	Conditions	Interventions
NCT03713320	Cobomarsen (MRG-106) vs. active comparator in subjects with Mycosis Fungoides (SOLAR)	Phase 2	Recruiting	MF	Cobomarsen vs. Vorinostat
NCT02953301	Resminostat for maintenance treatment of patients with advanced stage Mycosis Fungoides (MF) or Sézary Syndrome (SS) (RESMAIN)	Phase 2	Recruiting	MF/SS	Resminostat vs. Placebo
NCT02783625	Duvelisib in combination with either Romidepsin or Bortezomib in relapsed/refractory T-cell Lymphomas	Phase 1	Recruiting	CTCL and others	Duvelisib + Romidepsin or Duvelisib + Bortezomib
NCT01871727	E7777 in persistent and recurrent cutaneous T-Cell Lymphoma	Phase 3	Recruiting	MF/SS	E7777 (fusion protein that combines the IL-2 receptor binding domain with diphtheria toxin fragments; related to Denileukin Diftitox)
NCT02232516	Romidepsin and Lenalidomide in treating patients with previously untreated peripheral T-Cell Lymphoma	Phase 2	Recruiting	MF/SS and others	Romidepsin + Lenalidomide
NCT00466921	Lenalidomide in treating patients with relapsed Mycosis Fungoides/Sézary Syndrome	Phase 2	Active, not recruiting	MF/SS	Lenalidomide
NCT03409432	Brentuximab Vedotin and Lenalidomide in treating patients with Stage IB-IVB relapsed or refractory T-Cell Lymphoma	Phase 2	Recruiting	CTCL and others	BV + Lenalidomide
NCT02616965	Romidepsin combined with Brentuximab Vedotin in cutaneous T-cell Lymphoma	Phase 1	Recruiting	CTCL	Romidepsin + BV

ening of erythroderma and pruritus was observed. However, this side effect did not result in treatment discontinuation in any patient. Taken together, this study demonstrated durable responses and a favorable safety profile of pembrolizumab in pretreated MF and SS patients [30]. Ongoing studies are evaluating the efficacy of several PD1- and PD-L1 inhibitors such as pembrolizumab, nivolumab, durvalumab, atezolizumab and avelumab, either alone or in combination with other agents or radiation to treat MF and SS (Table 1).

Other promising future therapies

Due to limited space this article only briefly refers to duvelisib (IPI-145), an oral inhibitor of phosphatidylinositol 3-kinase (PI3K)- δ/γ isoforms. Its inhibition directly blocks malignant T-cell growth and modulates nonmalignant immune cells. Results of a phase I study investigating the efficacy and safety of duvelisib in relapsed PTCL and CTCL were recently published and revealed encouraging data with clinical activity and acceptable safety profile [31]. Several other agents are currently being assessed in MF/SS. A selection of these is summarized in Table 2.

Conclusion

The approval of BV and mogamulizumab for advanced and refractory MF and SS has broadened the therapeutic spectrum for this incurable disease group with poor prognosis. Lacutamab and PD-1/L-1 inhibitors have demonstrated encouraging results in phase 1 and phase 2 trials. More promising novel

therapeutic agents are currently undergoing clinical trial and will continue to expand the therapeutic options available in the management of advanced-stage MF and SS.

Take home message

The approval of BV and mogamulizumab has broadened the therapeutic spectrum for advanced and refractory MF/SS. Other potential therapies such as lacutamab and PD-1/L-1 inhibitors have shown promise.

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