New and emerging therapies in cutaneous T-cell lymphoma

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Abstract

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL) that typically presents in the early phase as inflammatory erythematous patches or plaques, with epidermotropism as the histopathological hallmark of the disease. Traditionally, in the early stages, non-aggressive options represent the first-line strategy: topical corticosteroids, phototherapy, radiotherapy, and occasionally adopting a "wait-and-see" approach for minimally symptomatic patients. In patients with advanced or recurrent disease, good results can be achieved with immune modifiers, chemotherapeutic agents, total skin irradiation, or extracorporeal photochemotherapy, and maintenance therapy is often required. The past decade has seen an expansion of therapies that can be used in this setting by increasing new therapeutic strategies. The key advancements coming from recently published trials are resumed in this article.

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Updates in the 2023 EORTC guidelines on cutaneous T-cell lymphoma

The European Organisation for Research and Treatment of Cancer (EORTC) released updated guidelines in 2023 regarding the management of cutaneous T-cell lymphoma (CTCL), reflecting significant advancements in treatment strategies and supportive care.[1] Major revisions from previous versions include the incorporation of new therapeutic agents, recommendations on the use of pegylated interferon α, and enhanced guidance on supportive therapy and care for older patients.

1. Incorporation of new therapeutic agents: chlormethine, brentuximab vedotin, and mogamulizumab have been integrated into the treatment armamentarium for CTCL. These agents offer additional options for patients.
2. Recommendations on Pegylated Interferon α (peg-IFN-α): with the withdrawal of previously available formulations of recombinant unpegylated interferons (IFN-α 2a, IFN-α 2b), the guidelines now advocate for the use of pegylated IFN-α 2a (peg-IFN-α 2a) as a replacement.
   - Studies have demonstrated the efficacy and tolerability of peg-IFN-α 2a in MF patients, with response rates and adverse effect profiles comparable to previous formulations.
   - While dose equivalents between pegylated and non-pegylated IFN-α have not been established, initiating treatment with 135-180 μg/week subcutaneously is recommended.
   - Close clinical and laboratory monitoring should accompany treatment, allowing for dose adaptation based on individual patient response and tolerance.
3. Supportive therapy and care for older patients: In the context of CTCL, common skin-related symptoms include pruritus and painful sensations, significantly impacting quality of life. Additionally, colonization of the skin by *Staphylococcus aureus* may exacerbate the disease. While measures to reduce bacterial colonization and infection risk are often employed, specific recommendations are lacking due to insufficient evidence. Therefore, decisions regarding supportive care for CTCL patients should be individualized, and further research in this area is encouraged.

Hypericin

Hypericin, naturally found in plants (*Hypericum* genus),[2] is tumoricidal as a stand-alone drug and with activation by visible light.[3] It is preferentially absorbed into malignant cells, particularly *in vivo*.[4] Visible light in the yellow-red spectrum (range, 500-650 nm) is expected to penetrate 1 to 2 mm into the skin and activate hypericin localized in the perinuclear region within the endoplasmic reticulum and Golgi apparatus.[5] Activated hypericin triggers the caspase-signaling cascade through reactive oxygen species, resulting in apoptosis via the mitochondrial pathway.[6]

Based on this biological rational, the FLASH study was developed as a phase 3 placebo-controlled, double-blind, multicenter randomized clinical trial conducted to evaluate the efficacy and safety of synthetic hypericin ointment PDT in patients with early-stage MF/CTCL (stages IA-IIA per international guidelines).[7] Including 169 patients, the study design provided that, in cycle 1, patients were randomized 2:1 to receive hypericin or placebo to 3 index lesions twice weekly for 6 weeks. In cycle 2, all patients received the active drug for 6 weeks to index lesions. In cycle 3 (optional), both index and additional lesions received active drug for 6 weeks. Topical hypericin PDT was more effective than placebo after one cycle of treatment for 6 weeks (index lesion response rate, 16% *vs.* 4%); responses increased to 40% after two cycles, 49% after three cycles, and were seen in patch and plaque lesions. Adverse events were primarily mild application-site skin reactions. Topical synthetic hypericin activated with visible light represents a novelty in therapy for early-stage MF/CTCL, and it is an effective and well-tolerated treatment.

Pimecrolimus

Topical calcineurin inhibitors have been approved for the treatment of atopic dermatitis, and although they are widely used off-label in other cutaneous disorders, these inhibitors are rarely used for mycosis fungoides. Topical calcineurin inhibitors bind macrophillin-12, resulting in the suppression of calcineurin activity and subsequent inhibition of the synthesis of inflammatory cytokines. The calcineurin pathway in patients with mycosis fungoides is often activated in mycosis fungoides whether or not the PLCG1 mutation is present.[8,9] Therefore, the use of targeted therapies with topical calcineurin inhibitors might theoretically be beneficial for patients with and without PLCG1 mutations. In phase 2, a multicenter, single-arm PimTo-MF study evaluated the activity and safety of topical pimecrolimus in patients with early mycosis fungoides across six medical centers in Spain.[10] Patients applied topical pimecrolimus 1% cream on their skin lesions twice daily for 16 weeks (1 g per 2% of body surface), with subsequent follow-up of 12 months. The study demonstrated the achievement of a clinical response in more than half of the patients (56%), especially in stages IA (54%) and IB (73%), but not in stage IIA (0%). Topical pimecrolimus was well tolerated, and no patient required a dose reduction or discontinued treatment due to unacceptable drug-related toxicity. About one-third of the patients experienced mild adverse reactions such as transitory mild burning or pruritus (grade 1). Ortiz-Romeo *et al.* claim that pimecrolimus 1% cream seems active and safe in patients with mycosis fungoides at an early stage.

Lacutamab

KIR3DL2 (CD158k) is a member of the highly polymorphic family of killer-cell immunoglobulin-like receptors, and it is expressed in more than 85% of patients with Sézary syndrome.[11] IPH4102 is a humanized, first-in-class monoclonal antibody that is designed to deplete KIR3DL2-expressing cells via antibody-dependent cell cytotoxicity and phagocytosis.[12] Bagot *et al.* reported the first-in-human, phase 1 study assessing IPH4102 in patients with relapsed or refractory cutaneous T-cell lymphoma with the aim of evaluating its safety and activity.[13] This international, first-in-human, open-label, phase 1 clinical trial included patients with a histologically confirmed relapsed or refractory primary cutaneous T-cell lymphoma with an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less, having received at least two previous systemic therapies. IPH4102 was administered intravenously with a dosage ranging from 0-0001 mg/kg to 10 mg/kg to evaluate the dose-limiting toxicities during the first 2 weeks of treatment as the primary endpoint. Global overall response by cutaneous T-cell lymphoma subtype was a secondary endpoint. As a result, no dose-limiting toxicities or IPH4102 immune-related adverse events were observed in the study and the safety committee recommended a fixed dose of 750 mg for the cohort expansion, corresponding to the maximum dose administered. The most common side effects were peripheral oedema (27%) and fatigue (20%), and the most severe was grade 3 lymphopenia (7%). Regarding effectiveness, a global overall response was achieved in 15 (43%) of 35 patients with Sézary syndrome. Current data on IPH4102 demonstrate that the drug is safe and shows encouraging clinical activity in patients with relapsed or refractory cutaneous T-cell lymphoma, particularly those with Sézary syndrome, and may become a new therapeutic option for these patients. A multi-cohort, phase 2 trial (TELLOMAK) is underway to confirm the activity in patients with Sézary syndrome and explore the role of IPH4102 in other subtypes of T-cell lymphomas that express KIR3DL2.

Resminostat

HDAC inhibitors (HDACi) target epigenetic changes in CTCL and have been evaluated within the last decades thanks to their antitumor and anti-angiogenic properties.[14,15] From 2017 to 2022, the RESMAIN trial investigated the efficacy of resminostat in a placebo-controlled phase 2b study.[16] In total, 201 patients with MF (n=164) or SS (n=37) have been enrolled and randomized to resminostat or placebo group. The treatment schedule involved oral intake on days 1-5 followed by a 9-day treatment-free period in 14-day circles. Resminostat showed a beneficial effect on PFS *versus* placebo (median 8.3 *vs.* 4.2 months) but failed to improve health-related quality of life. So far, HDACi has not been implemented in the latest update of the EORTC consensus recommendation, as the official results have not been published yet.

Immunotherapies and novel targets

Nowadays, it has been extensively demonstrated that CTCLs are immunogenic malignancies, and tumor cells, like other cancer cells, elude immune surveillance.[17] In mycosis fungoides (MF)/Sezary syndrome (SS), the cellular immune system undergoes some alterations. Primarily, a reduction in T-helper type 1 (TH1) activity is evidenced by a diminished production of pro-inflammatory cytokines IFN-α, IFN-γ, and interleukin (IL)-12.[18] Consequently, an increase in TH2 activity is observed, marked by elevated levels of TH2 cytokines such as IL-4, IL-5, and IL-10. These cytokines are known to inhibit the production of TH1-type cytokines, leading to a TH2-dominant immune environment. The TH1-driven anti-tumor CD8 cytotoxic response is then diminished together with the number of dendritic cells and their production of IL-12 and IFN-α in MF/SS.[19] These alterations collectively contribute to immune evasion in CTCL. Another characteristic feature of an immune-evasive tumor microenvironment is the presence of hyporeactive or exhausted T cells.[20] The expression of inhibitory molecules like programmed death receptor-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is indicative of

exhausted T cells. Previous reports show evidence of expression for both PD-1 and its ligands; however, little is still known about the extent of PD-1 activity in malignant *versus* non-malignant T cells in MF/SS.[21-23] It is well known that the engagement of PD-1 with its ligands PD-L1 and PD-L2 prevents T-cell activation and proliferation, leading to a reduction of the immune response. Similarly, overexpression of the other inhibitory checkpoint receptor, the B7-ligand known as CTLA-4, has been proven to weaken immune surveillance in tumors.[24,25] This is why blocking this checkpoint has become a pivotal aspect in the field of immuno-oncology. Studies have been carried out to thoroughly understand PD-1 and CTLA-4 expression in cutaneous lymphomas.[26,27] In a phase 1 study, Lesokhin *et al.* reported good tolerability in 81 patients with hematologic malignancies, including MF and PTCL, with an overall response rate (ORR) of 15% in MF and 40% in PTCL.[28] Pembrolizumab was investigated in a phase 2 study involving 24 pre-treated MF and SS patients, showing an ORR of 38% with two complete responses (CR) and seven partial responses (PR).[29] Additionally, a phase 1b study explored pembrolizumab in combination with pralatrexate or decitabine, revealing promising responses, especially in the triple combination arm.[30] Overall, PD-1 inhibitors can play a role in the treatment of a subset of patients with MF/SS. However, future work is needed to identify the characteristics of responders *versus* non-responders and to determine how PD-1 blockade affects malignant *versus* non-malignant T cells in MF/SS. As for CTLA-4, its efficacy in CTCL has yet to be determined. In a single case report, a 44-year-old male with MF and melanoma exhibited a complete resolution of MF cutaneous lesions after treatment with ipilimumab for advanced melanoma.[31] In another case, a patient with SS had a tragic and rapid disease progression after an initial period of six weeks of response.[32] The 2023 EORTC guidelines indicate that, based on the existing study results, no definitive conclusion regarding the clinical efficacy of anti-PD1/PD-L1 can be drawn.[33]

Anti-CD47

High expression of cluster of differentiation (CD) 47 on tumor cells is believed to suppress phagocytosis by interaction with a signal regulatory protein (SIRPα) on macrophages and dendritic cells.[34] This overexpression is common in solid and hematological tumors, including acute leukemia, non-Hodgkin's lymphoma (NHL), and colorectal and ovarian cancers. It has been evidenced that its expression often correlates with an aggressive phenotype and an overall poor clinical prognosis. Hence, inhibiting it could boost macrophage phagocytic activity, thereby fortifying defense against cancer cells. Several ligand-blocking monoclonal antibodies (mAbs) engineered receptor decoys and bispecific agents that disrupt the CD47-SIRPα axis have demonstrated activity in preclinical models from a diverse spectrum of neoplasms, highlighting impaired tumor growth, inhibition of metastatic spread, and tumor regression.[35-37] TTI-621 is a soluble recombinant fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG1. Preliminary results in a phase 1 study of patients with CTCL demonstrated an improvement of lesions in 90% of the patients. More importantly, in patients with circulating Sézary cells, all patients experienced a reduction in circulating cell number after only one tumor injection.[38] Another agent in clinical development is magrolimab, an anti-CD47 antibody. A Phase 1b/2 trial is investigating the possible benefits and/or side effects of magrolimab when given in combination with mogamulizumab in treating patients with stage IB-IV MF or SS types of T-cell lymphoma that has come back (relapsed) or does not respond to treatment (refractory).[39] Additionally, this anti-CD47 antibody Hu5f9-G4 is being evaluated in a Phase 1b/2 trial in combination with rituximab or rituximab + chemotherapy in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma.[40]

Anti-CD70

CD70 is a member of the tumor necrosis factor receptor superfamily with unique properties that make it an ideal target for cancer therapy. It interacts with a ligand, CD27, and it's only transiently expressed on activated T- and B-lymphocytes, mature killer cells, and mature dendritic cells, while it has limited expression on normal, nonimmune cells.[41,42] Interactions between CD70 and CD27 have been evidenced as a costimulatory signal in T- and B-lymphocyte activation and as an induction to lymphocytic proliferation. However, until now, the potential benefit of targeting CD70 in T-cell lymphomas has not been established yet. Chi-Heng Wu *et al.* have investigated the expression of CD70 in cutaneous and systemic T-cell lymphomas, and they conducted preclinical studies of SGN-CD70A, a CD70-directed antibody-drug conjugate (ADC), using patient-derived xenograft cutaneous T-cell lymphoma (CTCL PDX) models. They found that CD70 is highly expressed in T-cell lymphomas, especially in CTCL. Additionally, they demonstrated that SGN-CD70A inhibited cell growth and induced apoptosis in CD70-expressing CTCL cell lines and primary tumor cells.[43]

References

1. Latzka J, Assaf C, Bagot M, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. Eur J Cancer 2023;195:113343.
2. Durán N, Song PS. Hypericin and its photodynamic action. Photochem Photobiol 1986;43:677-80.
3. Blank M, Lavie G, Mandel M, et al. Antimetastatic activity of the photodynamic agent hypericin in the dark. Int J Cancer 2004;111:596-603.
4. Kamuhabwa AA, Cosserat-Gerardin I, Didelon J, et al. Biodistribution of hypericin in orthotopic transitional cell carcinoma bladder tumors: implication for whole bladder wall photodynamic therapy. Int J Cancer 2002;97:253-60.
5. Vandenbogaerde AL, Cuveele JF, Proot P, et al. Differential cytotoxic effects induced after photosensitization by hypericin. J Photochem Photobiol B 1997;38:136-42.
6. Garg AD, Agostinis P. ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses. Photochem Photobiol Sci 2014;13:474-87.
7. Kim EJ, Mangold AR, DeSimone JA, et al. Efficacy and Safety of Topical Hypericin Photodynamic Therapy for Early-Stage Cutaneous T-Cell Lymphoma (Mycosis Fungoides): The FLASH Phase 3 Randomized Clinical Trial. JAMA Dermatol 2022;158:1031-9.
8. Choi J, Goh G, Walradt T, et al. Genomic landscape of cutaneous T cell lymphoma. Nat Genet 2015;47:1011-9.
9. Vaqué JP, Gómez-López G, Monsálvez V, et al. PLCG1 mutations in cutaneous T-cell lymphomas. Blood 2014;123:2034-43.
10. Ortiz-Romero PL, Maroñas Jiménez L, Muniesa C, et al. Activity and safety of topical pimecrolimus in patients with early stage mycosis fungoides (PimTo-MF): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2022;9:e425-33.
11. Battistella M, Leboeuf C, Ram-Wolff C, et al. KIR3DL2 expression in cutaneous T-cell lymphomas: expanding the

spectrum for KIR3DL2 targeting. Blood 2017;130:2900-2.
12. Marie-Cardine A, Viaud N, Thonnart N, et al. IPH4102, a humanized KIR3DL2 antibody with potent activity against cutaneous T-cell lymphoma. Cancer Res 2014;74:6060-70.
13. Bagot M, Porcu P, Marie-Cardine A, et al. IPH4102, a first-in-class anti-KIR3DL2 monoclonal antibody, in patients with relapsed or refractory cutaneous T-cell lymphoma: an international, first-in-human, open-label, phase 1 trial. Lancet Oncol 2019;20:1160-70.
14. Lai P, Wang Y. Epigenetics of cutaneous T-cell lymphoma: biomarkers and therapeutic potentials. Cancer Biol Med 2021;18:34-51.
15. Foss F, Advani R, Duvic M, et al. A Phase II trial of Belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol 2015;168:811-9.
16. Stadler R, Scarisbrick JJ. Maintenance therapy in patients with mycosis fungoides or Sézary syndrome: A neglected topic. Eur J Cancer 2021;142:38-47.
17. Chong BF, Wilson AJ, Gibson HM, et al. Immune function abnormalities in peripheral blood mononuclear cell cytokine expression differentiates stages of cutaneous T-cell lymphoma/mycosis fungoides. Clin Cancer Res 2008;14:646-53.
18. Shalabi D, Bistline A, Alpdogan O, et al. Immune evasion and current immunotherapy strategies in mycosis fungoides (MF) and Sézary syndrome (SS). Chin Clin Oncol 2019;8:11.
19. Vowels BR, Lessin SR, Cassin M, et al. Th2 cytokine mRNA expression in skin in cutaneous T-cell lymphoma. J Invest Dermatol 1994;103:669-73.
20. Zarour HM. Reversing T-cell dysfunction and exhaustion in cancer. Clin Cancer Res 2016;22:1856-64.
21. Kantekure K, Yang Y, Raghunath P, et al. Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. Am J Dermatopathol 2012;34:126-8.
22. Roccuzzo G, Giordano S, Fava P, et al. Immune check point inhibitors in primary cutaneous t-cell lymphomas: biologic rationale, clinical results and future perspectives. Front Oncol 2021;11:733770.
23. Samimi S, Benoit B, Evans K, et al. Increased programmed death-1 expression on CD4+ T cells in cutaneous T-cell lymphoma: implications for immune suppression. Arch Dermatol 2010;146:1382-8.
24. Jin HT, Ahmed R, Okazaki T. Role of PD-1 in regulating T-cell immunity. Curr Top Microbiol Immunol 2011;350:17-37.
25. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med 2016;8:328rv4.
26. Schietinger A, Greenberg PD. Tolerance and exhaustion: defining mechanisms of T cell dysfunction. Trends Immunol 2014;35:51-60.
27. Quaglino P, Fava P, Pileri A, et al. Phenotypical Markers, Molecular Mutations, and Immune Microenvironment as Targets for New Treatments in Patients with Mycosis Fungoides and/or Sézary Syndrome. J Invest Dermatol 2021;141:484-95.
28. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol 2016;34:2698-704.
29. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and sézary syndrome: a multicenter phase II study. J Clin Oncol 2020;38:20-8.
30. Marchi E, Ma H, Montanari F, et al. The Integration of PD1 Blockade With Epigenetic Therapy is Highly Active and Safe in Heavily Treated Patients With T-Cell Lymphoma (PTCL) and Cutaneous T-Cell Lymphoma (CTCL). J Clin Oncol 2020;38:8049.
31. Bar-Sela G, Bergman R. Complete regression of mycosis fungoides after ipilimumab therapy for advanced melanoma. JAAD Case Rep 2015;1:99-100.
32. Sekulic A, Liang WS, Tembe W, et al. Personalized treatment of Sézary syndrome by targeting a novel CTLA4:CD28 fusion. Mol Genet Genomic Med 2015;3:130-6.
33. Latzka J, Assaf C, Bagot M, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. Eur J Cancer 2023;195:113343.
34. Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 2009;138:286-99.
35. Liu X, Pu Y, Cron K, et al. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. Nat Med 2015;21:1209-15.
36. Ring NG, Herndler-Brandstetter D, Weiskopf K, et al. Anti-SIRPα antibody immunotherapy enhances neutrophil and macrophage antitumor activity. Proc Nat Acad Sci United States Am 2017;114:E10578-85.
37. Weiskopf K, Jahchan NS, Schnorr PJ, et al. CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer. J Clin Invest 2016;126:2610-20.
38. Querfeld C, Thompson JA, Taylor MH, et al. Intralesional TTI-621, a novel biologic targeting the innate immune checkpoint CD47, in patients with relapsed or refractory mycosis fungoides or Sézary syndrome: a multicentre, phase 1 study. Lancet Haematol 2021;8:e808-17.
39. ClinicalTrials.gov Identifier: NCT04541017
40. ClinicalTrials.gov Identifier: NCT02953509
41. Bullock TN, Yagita H. Induction of CD70 on dendritic cells through CD40 or TLR stimulation contributes to the development of CD8+ T cell responses in the absence of CD4+ T cells. J Immunol 2005;174:710-7.
42. Lens SM, Baars PA, Hooibrink B, et al. Antigen-presenting cell-derived signals determine expression levels of CD70 on primed T cells. Immunology 1997;90:38-45.
43. Wu CH, Wang L, Yang CY, et al. Targeting CD70 in cutaneous T-cell lymphoma using an antibody-drug conjugate in patient-derived xenograft models. Blood Adv 2022;6:2290-302.