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REVIEW

Systemic therapy for cutaneous T-cell lymphoma: who, when, what, and why?

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ABSTRACT

Introduction: CTCL are rare neoplasms. Optimal care requires integrated use of diagnostic and treatment modalities spanning multiple specialties. Current instruments for patient risk stratification and disease measurement across all anatomical compartments are suboptimal. A common treatment dichotomy between early (Dermatology) and advanced stage (Hematology-Oncology) has hindered accrual of long term outcome data. Thus, important facts about natural history, such as frequency and determinants of stage progression, and the impact of specific treatment modalities on these endpoints, are not known.

Areas covered: One of the most important decisions in the management of CTCL is when to start systemic therapy and what agents to use. This review provides background information to understand why systemic therapy is needed and what goals are currently achievable.

Expert commentary: Risk-adapted approaches, based on better knowledge of host and tumor biology, and more accurate disease measurement tools are needed to optimize the use of specific systemic therapies.

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1. Introduction

Cutaneous T-cell lymphomas (CTCL) constitute about 70–75% of the primary cutaneous lymphomas, with mycosis fungoides (MF) being the most common subtype [1–3]. The prognosis of CTCL depends on the specific disease entity and the stage at which it presents. MF is characterized by an indolent course, generally with a stepwise progression toward greater disease burden in the skin, followed by extracutaneous dissemination in a subset of patients [4]. Sezary syndrome (SS) is a more aggressive type of CTCL. Patients with SS have erythroderma (i.e. rash affecting >80% body surface area [BSA]), lymphadenopathy, and high numbers of circulating neoplastic CD4+ T cells in the peripheral blood [5]. According to the revised ISCL/EORTC classification for MF/SS, SS is implicitly considered an advanced stage of MF (Stage ≥IVA1), despite the fact that in many cases, it develops *de novo* and may have a different cell of origin than MF [6]. Whether *de novo* SS should be recognized as a stand-alone T-cell neoplasm, with distinct diagnostic, staging, and response criteria, is a subject of controversy, especially because the distinction between *de novo* and *secondary* SS is not always easy [7]. Other so-called non-MF/SS subtypes of CTCL, such as aggressive epidermotropic CD8+ T-cell lymphomas, primary cutaneous gamma delta T-cell lymphomas, and peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) behave aggressively irrespective of stage and therefore need systemic treatment from the time of diagnosis [8]. In contrast, CD30+ lymphoproliferative disorders, CD4+ small medium pleomorphic T-cell lymphoproliferative disorder, and its variant CD8+ lymphoid proliferation of acral sites are typically indolent with a favorable prognosis and excellent response to skin-directed therapy (SDT) [8]. This review will focus on the systemic management strategy for patients with MF and SS. In addition to developing more effective therapies for advanced stage patients, there is an urgent need to better identify the subset(s) of early stage MF patients at higher risk of stage progression and large cell transformation (LCT) and to determine the differential impact of specific forms of systemic therapy (and combinations) in these patients at different time points in the natural history of the disease.

2. Framing the clinical research questions

2.1. The existing practice models

The management of MF/SS continues to be challenging due to the lack of good risk stratification tools, accurate and reproducible quantification of disease burden in all anatomical compartments (skin, blood, lymph nodes, and visceral organs),

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and effective therapies capable of achieving profound, hence durable, cytoreduction. These challenges are compounded by the fact that MF and SS is rare neoplasms and is optimally managed in an integrated practice environment, spanning multiple specialties (dermatology, medical oncology, radiation therapy, dermato-, and/or hematopathology), which is rarely available even in tertiary care health centers and academic institutions. Furthermore, reimbursement models for multimodality clinical care in CTCL in the United States remain outdated (i.e. based on quantity rather than quality of the care provided) and there is currently no economic incentive supporting the establishment and operation of multispecialty CTCL clinics [9]. Finally, the long-standing dichotomy, predominant in the United States, where most early stage patients are managed by dermatology and most advanced stage patients by hematology–oncology, has hindered the development of a more integrated approach to patient care and a better understanding of the disease's natural history. In a conventional practice setting, dermatologists may not have the opportunity to observe the long-term impact of their initial therapeutic choices on stage progression, LCT, and survival. Conversely, some hematologists and medical oncologists, treating a patient with rapidly progressing tumor lesions and nodal disease, may be compelled to select cytotoxic chemotherapy approaches that not only produce short-lived responses but also cause additional immune suppression. The continuous need for optimal SDT, and its integration in systemic therapy strategies, can also be overlooked.

While the creation of a small number of highly specialized academic centers has been instrumental in the development of new therapies and in the optimization of care for patients with MF/SS, 'expert-driven care' has also led to the establishment of institution-specific practice patterns, with significant differences in therapeutic strategy and in the selection and utilization of specific treatment modalities. As a consequence, though informative, outcome analyses in MF/SS have consisted of retrospective single institution studies that reflect the unique approach of each team of experts and are not necessarily applicable to community-based practice. Thus, our understanding of the natural history of these neoplasms at the population level has remained biased and incomplete and the pivotal points in the clinical course of MF/SS where a timely and effective therapeutic intervention may alter the evolution or progression of this malignancy are not known, particularly in patients with 'intermediate' stages of MF (i.e. IB–IIB).

2.2. Diversifying clinical outcome end points

Beyond overall survival (OS), the most relevant clinical end points to assess the impact of therapy in MF/SS remain to be defined. For example, the predictive value of response rate (RR) and progression-free survival (PFS) vis-à-vis long-term outcome is unclear. Alternative natural history benchmarks and clinical/biological end points of significant interest, but more difficult to capture, are (1) the long-term (>10 years) rates of progression from early (IA–IB) to advanced (≥IIB) stage and the impact of specific therapies (including the differential effect of single vs. combined modality therapy) on such rates, (2) the molecular and immunological risk factors for stage progression, and (3) the biological factors affecting the development and tempo of limited versus generalized tumors stage disease.

2.3. What are the goals of systemic therapy?

Consensus guidelines regarding the treatment of MF and SS have been proposed by various organizations, including the National Comprehensive Cancer Network (NCCN) [10], the European Organization for Research and Treatment of Cancer (EORTC) [11], and the European Society of Medical Oncology [12]. All guidelines emphasize the fact that MF is a chronic disease with a relapsing course and the main goals of therapy are long-term disease control, effective symptom management, and prompt treatment of life-threatening disease. While SDT is adequate and sufficient life-long in many patients with very early stage disease (IA), a substantial fraction of early stage patients with more extensive skin involvement (IB) fails SDT and needs to start systemic therapy [13,14]. Systemic therapy, therefore, could be envisioned to have two primary goals in patients with MF/SS: (1) preventing or delaying progression to tumor stage (IIB) in patients with more extensive early stage disease (IB) who fail repeated courses of SDT; and (2) achieving durable, high-quality responses, and consequently improve survival, in patients with advanced stage disease (IIB–IVB). It is remarkable that, 30 years after the introduction of the first clinically effective systemic therapy (i.e. interferon) for the treatment of MF/SS [15], our ability to benchmark progress toward these goals remains in doubt. The median 5-year survival of patients with very advanced stage MF (stage IVA–B) remains quite poor (~2 years) and the long-term impact of individual therapies on stage progression and survival in early stage MF is still unknown [16–18].

2.4. How are the goals of systemic therapy to be achieved?

The selection of specific systemic therapies has traditionally been guided by the principle of 'no immune harm.' Initially based on empirical but well-documented observations [19], and now further supported by a recent large retrospective study [20], it postulates that immunostimulatory (e.g. interferons) or immune-preserving (retinoids, histone deacetylase [HDAC] inhibitors) therapies result in more durable responses than cytotoxic chemotherapy. This important guiding principle, however, remains to be prospectively validated and should not prevent clinicians from choosing alternative options in selected patients. For example, judicious use of severely lymphodepleting – and therefore highly immunosuppressive – monoclonal antibodies, such as alemtuzumab, can produce remarkably long responses and be safely administered in the appropriate patient subsets (i.e. SS) [21–25]. Likewise, short-term use of cytotoxic chemotherapy can be life-saving in some patients and allow them to proceed to allogeneic hematopoietic stem cell transplant (HSCT) [26]. Relapse after each line of therapy, however, is the rule and the use of maintenance strategies has been routinely adopted to decrease the risk of relapse or delay progression, despite

lack of prospective data [27]. Currently, allogeneic HSCT is the only known potentially curative treatment, but patient selection and optimal timing for transplant remain challenging tasks [28].

2.5. Challenges in defining and measuring objective responses

Until recently, the lack of consensus in defining clinical end points and disease response criteria for MF/SS created substantial problems in comparing treatment efficacy among studies. The criteria proposed by Olsen et al. [29] represent an attempt to harmonize response assessment but are still burdensome and suboptimal, especially in the assessment of blood involvement (B stage). They are predominantly used for disease assessment on clinical trials and are seldom used for disease evaluation or treatment decisions in clinical practice. Assessment of B stage, even with flow cytometry, is highly variable from laboratory to laboratory, a fact reflected by the now common practice of scoring blood responses in clinical trials only through a centralized lab. The current ISCL/EORTC criteria remain vague, offering more than one option to immunophenotypically define and track the abnormal population of T cells (percent CD4+CD7−, percent CD4+CD26−, and CD4/CD8 ratio). More accurate methodologies to quantify the tumor clone in SS, such as Vb flow cytometry [30] and high-throughput sequencing [31] are not discussed or included in the current ISCL/EORTC criteria. Finally, the current TNMB staging system does not accurately reflect skin tumor burden (T stage), which at this time is better assessed with the modified Severity Weighted Assessment Tool (mSWAT) [32,33] and does not include valuable information such as presence of folliculotropism (FT) and/or LCT, which are important for treatment decisions [34–36].

Likewise, inconsistencies remain in the definition and use of disease progression end points and in their impact on clinical decision-making. *Stage progression* represents an increase in either the TNMB stage of the patient (i.e. T1 > T2) or in the composite ISCL/EORTC stage (IIB > III), whereas *disease progression* or *relapse* (with or without stage progression) has been defined as loss of response or development of new sites of disease after a complete response, respectively. In the skin, disease progression corresponds to an increase in the skin score (typically mSWAT) of ≥25% from baseline [29]. Neither of these clinical progression end points (stage or disease), however, is always helpful in guiding treatment decisions, and the threshold for initiating systemic therapy varies substantially among clinicians, including experts. For example, the development of new patch lesions covering 2% BSA (or an increase in mSWAT from 0 to 2) in a patient in CR after phototherapy meets criteria for relapse but does not necessarily represent an indication to start systemic therapy. Likewise, an increase from 8% BSA (IA) to 16% BSA (IB) patch/plaque disease, while fitting the definition of stage progression, does not imply a need for systemic therapy. The search for alternative and potentially more informative efficacy end points for MF/SS has recently led some to propose time to next treatment (TTNT) [20], defined as the time interval between the date of initiation of one systemic therapy and the date of initiation of the next systemic therapy. TTNT, therefore, reflects the clinicians' and patients' composite assessments of treatment efficacy, tolerability, and overall efficacy of each line of therapy, providing a valuable reflection of the quality and durability of the clinical benefit.

2.6. The urgent need for better risk assessment

Along with the search for alternative efficacy end points and for additional natural history benchmarks in MF/SS, studies have aimed at identifying more discriminatory risk stratification tools to assess prognosis. In light of their retrospective design, selection bias, lack of treatment homogeneity, inconsistent definition of prognostic variables, and incomplete data sets, the reproducibility of these studies, and therefore their impact, has been poor [37,38]. More recently, however, a large retrospective study of the Cutaneous Lymphoma International Consortium (CLIC), focused on patients with advanced stage MF/SS (≥IIB), was published [39]. This important study presented a survival analysis on 1275 advanced stage MF/SS patients from 29 centers and, while offering a valuable and more robust analysis of candidate prognostic factors in a very large cohort of patients, it also highlighted the difficulty of obtaining complete data sets, and therefore adequate statistical power, in a retrospective analysis. This study has served as the foundation for the planning of two prospective CLIC studies of prognostic factors in early-stage and advanced-stage MF/SS (Pro-CLIPI) that are currently ongoing.

3. Treatment approach

MF is a clinico-pathological diagnosis that often requires immunophenotypic and molecular corroboration for confirmation of diagnosis [4]. Multiple biopsies are usually necessary before making a definitive diagnosis in early-stage disease. While the modified ISCL/EORTC staging system for MF/SS, based on tumor extent, nodal, metastasis, blood (TNMB) involvement is used to classify the disease into early (I–IIA) and late (IIB–IV) stages [5], other factors, such presence or absence of FT and LCT are also considered in making treatment decisions. Patient's age, comorbidities, and individual preferences for specific treatment options should also be considered. Finally, cost and logistical arrangements also influence treatment decisions.

3.1. Early stage MF

Early stage (IA–IIA) MF, in absence of FT or evidence of LCT, is mostly amenable to SDT. SDT regimens include topical steroids, topical cytotoxic agents (nitrogen mustard), topical immunomodulators (bexarotene, imiquimod), phototherapy (NBUVB, psoralen + UVA), and radiation (including TSEBR). Limited randomized data suggests that single-agent topical therapy is as good as combination therapy with electron beam radiation and chemotherapy in early-stage disease [40]. However, most patients receiving SDT eventually relapse and require additional treatment. For example, among patients with early-stage MF, Herrmann et al. observed a median

duration of response (DOR) of 43 months with PUVA therapy [41]. With TSEBR, the 5-year relapse-free survival in 241 MF patients was 56% for stage IA, 25% for stage IB, 13% for stage IIA, and only 2% for stage IIB [42]. Due to their significant heterogeneity, the outcomes reported by these studies cannot be meaningfully compared and the data only highlight that fact that most early-stage patients receiving SDT relapse or progress. Among those with a CR to topical nitrogen mustard, Kim et al. reported a median time to relapse of 12 months (range 1–60 months) in stages IA and IB [43]. These data show that even in patients with early-stage disease achieving very good responses, SDT does not provide a curative strategy. However, there are also no compelling data that the addition of systemic agents, including interferon and bexarotene, enhances the overall efficacy of phototherapy, delays disease progression, or prolongs survival in early-stage disease [44]. Identification of prognostic factors other than tumor staging is needed to identify early-stage MF patients who might benefit from early introduction of systemic therapy.

3.2. Advanced-stage MF

Patients with MF stage >IIB, with tumor lesions, erythroderma, and blood, nodal, and/or visceral involvement, need prompt initiation of systemic treatment. Most treatments are primarily aimed at achieving and maintaining disease remission and good quality of life. There is however a lack of comparative studies for various systemic therapeutic agents. Retrospective comparisons of available efficacy data are difficult because of great variability in the inclusion and response criteria. As noted, TTNT may be a more relevant and reproducible objective end point for retrospective analysis of treatment outcome for MF/SS [20]. Systemic agents used for treatment of MF/SS can be classified as chemotherapeutic agents, biological response modifiers (interferon, bexarotene, HDACi), monoclonal antibodies (alemtuzumab, mogamulizumab, brentuximab), HSCT, and extra corporeal photopheresis (ECP). No single regimen is known to be superior to others in overall response rate (ORR) or duration of response.

3.3. Chemotherapy

Published data suggest good RRs in patients receiving chemotherapy for treatment of MF/SS (Table 1) [9]. The duration of response, however, is usually very short, with the majority of patients witnessing quick relapses post-chemotherapy, unless the remission is maintained by adding a non-chemotherapeutic agent [45]. The TTNT is short and often similar for single agent versus multi-agent chemotherapy [20]. Studies show better survival in patients treated with less aggressive regimens than multi-agent chemotherapy, due to the associated toxicities [45].

In a recent retrospective analysis, Hughes et al. compared the efficacy of various chemotherapy regimens used in the treatment of patients with MF/SS at a single institution [20]. They reported a median TTNT of 3.9 months for all chemotherapy regimens in a cohort of 144 patients. Of all the chemotherapy regimens analyzed, CHOP-like combinations had the longest TTNT (5.7 months) while fludarabine and high-dose methotrexate-based regimens had the shortest TTNT (2.2 and 2.1 months, respectively). Predictably, the TTNT was longer if chemotherapy was given as a first-line treatment as compared to mid (second to fourth) and late (fifth and later) line treatment.

Pralatrexate is a novel antifolate with higher affinity for the reduced folate carrier and therefore able to achieve higher intracellular concentrations in cancer cells [53]. Pralatrexate was approved by the US FDA for the treatment of relapsed/refractory T-cell lymphoma on the basis of a pivotal multicenter international (PROPEL) study that enrolled 109 efficacy-eligible patients, including patients with refractory, transformed MF [54]. As a result of this study, pralatrexate was later evaluated in 54 patients with relapsed or refractory (R/R) CTCL (stage ≥IB MF, SS, and pcALCL) by Horwitz et al. using various doses and schedules of administration [55]. Evidence of tMF was not required for enrollment. After clinical activity was observed in the dose-finding cohort of 31 patients, the dosing schedule that combined the best safety with a meaningful RR was identified as 15 mg/m^2/week × 3 weeks every 28 days [55]. A total of 29 patients (all later evaluable) were treated with this dosing regimen, with an ORR of 45% (13/29:

Table 1. Selected studies of chemotherapy in MF/SS.

Regimen	Number of patients (*n*)	ORR	Median PFS	Comments
EPOCH [46]	15	80% (95% CI, 52–96%)	8 months (range, 3–22 months)	Patients were treated with gCSF support and TMP/SMX prophylaxis in addition to a median of 5 cycles of EPOCH (range, 1–9 cycles)
Fludarabine + cyclophosphamide [47]	6	83%	10 months	Patients who received at least 3 cycles of treatment
Fludarabine + interferon [48]	35	51% (95% CI, 35–70%)	5.9 months	Patients were treated with fludarabine 25 mg/m^2 intravenously and IFN 5 MIU/m^2 for up to 8 cycles
Gemcitabine [49]	25	48%	13.1 months	At least 3 cycles of treatment were administered
Pegylated liposomal doxorubicin [50]	34	88%	Not stated	EFS was 12 ± 9.5 months, and DFS was 13.3 ± 10.5 months (n = 16 patients)
Low-dose methotrexate [51]	60	33%	Not stated	The median time-to-treatment failure for the 60 patients with stage T2 disease was 15 months (95% CI, 9–20 months)
Pralatrexate [52]	12	25% per independent central review (n = 3); 58% (n = 7) per investigator assessment	1.7 months	Patients were treated with a median of 10 pralatrexate doses. Discrepancy of ORR was attributed to challenges with photo-documentation of cutaneous lesions

ORR: overall response rate; PFS: progression free survival; EPOCH: etoposide, prednisone, oncovin (vincristine), doxorubicin.

1 CR, 12 PR). Toxicities at the selected dosing regimen were mild and consisted or grade 1 or 2 fatigue, nausea, mucositis, fever, anemia, and epistaxis.

Two prospective Phase II studies of pegylated liposomal doxorubicin (PLD) have shown evidence of single agent activity in CTCL. In a European study [56], an ORR of nearly 41%, with 3 complete responses (CRs) was observed in 49 patients with stage IIA–IVB MF treated with 20 mg/m^2 IV on D1 and D15 every 28 days. In a second Phase II study [57], 37 patients with stage IB–IV disease received 20 mg/m^2 IV every 2 weeks for 16 weeks, followed by maintenance bexarotene. The ORR in 34 assessable patients was 41%, with 2 CRs and 12 partial responses. The main toxicities of PLD include myelosuppression, GI symptoms, hand-foot syndrome, and alopecia.

3.4. Retinoids

Bexarotene is a *rexinoid* (RXR receptor-binding retinoic acid derivative) that was FDA approved for the treatment of relapsed and refractory CTCL in 1999. In the pivotal study, oral bexarotene produced dose-dependent objective responses, with 300 mg/m^2 given once daily being the optimal dose [58,59]. The most common dose-limiting adverse effects associated with treatment include hypertriglyceridemia, central hypothyroidism, liver toxicity, leukopenia, and phototoxicity. Combinations with skin-directed regimens and other systemic agents is routinely used and may help achieve better RRs and prolonged remissions at a lower dose and toxicity, but the superiority of combination therapies has never been demonstrated. Commonly used combinations include bexarotene with nbUVB, PUVA, IFNs, or extracorporeal photopheresis (ECP). Combinations of bexarotene with methotrexate, vorinostat, or gemcitabine have been explored, but have been associated with an increased rate of adverse events (AEs) (hematologic as well as non-hematologic) [60–62]. Most studies reporting combination treatments are however not controlled and do not report the same end points or response criteria and are difficult to compare.

3.5. Interferons

Both interferon alfa (IFNα) [63–65] and interferon gamma (IFNγ) [66,67] are active in CTCL, but IFNα is the best studied in the treatment of MF/SS. Several clinical trials have reported ORRs ranging from 29% to 80% with the use of IFNα [68]. These RRs, however, are difficult to compare with those reported for more recently approved drugs. The recommended dose and duration of treatment with IFNα is largely institution-based. Most clinicians prefer to start at a lower dose (1–2 million units s.c. three times a week) and gradually increase the dose over several weeks, as tolerated. In a small, retrospective study (N = 17) higher RRs as well as more frequent myelosuppression and liver toxicity were seen with the pegylated form as compared to the non-pegylated form of IFNα, in combination with PUVA, possibly due to the longer half-life of the pegylated molecule [69]. Combination treatment of IFNα with bexarotene, phototherapy, TSEBT, or ECP have been proposed to be additive, if not synergistic (Table 3). However, the superiority of combinations has never been proven. In the retrospective analysis by Hughes et al, treatment with IFNα was associated with the longest duration of response (TTNT = 8.7 months) that was significantly greater as compared to chemotherapy (TTNR = 3.9 months) [20].

3.6. HDAC inhibitors

HDACs are a family of enzymes that target both histone and nonhistone proteins and are key components of many nuclear protein complexes affecting the cell's chromatin state and the coordinated expression of genes that regulate cell proliferation and apoptosis [70]. HDACs are divided into three families (classes) based on their homology to yeast HDAC proteins [71]. Aberrant histone deacetylation has been implicated in cancer development, generally associated with the silencing of tumor suppressor genes [72]; therefore, inhibiting the enzymatic activity of HDACs represents an attractive cancer-treatment strategy [73]. Romidepsin, vorinostat, and belinostat are three HDAC inhibitors (HDACi) that have been FDA approved for the treatment of CTCL (romidepsin and vorinostat) or PTCL (romidepsin and belinostat). Romidepsin is a class I HDACi that induces re-expression of p21 in cancer cells, leading to apoptosis. Two large international phase II studies showed efficacy and good tolerability of romidepsin in CTCL, leading to FDA approval. In one study, romidepsin was administered on day 1, 8, and 15 of a 28-day cycle in 71 patients with R/R CTCL [74]. The ORR was 34% with 6% complete responses. Median time to response was 8 weeks and the median DOR was 15 months. Whittaker et al. treated 96 patients with R/R CTCL with single-agent romidepsin observing an ORR of 34% [75]. It is important to note that in these studies, different methods were used to assess clinical response. The most common AEs were fatigue, nausea, vomiting, and thrombocytopenia.

Vorinostat is an organic hydroxamic acid that inhibits both class I and II HDACs and was FDA approved for the treatment of CTCL in 2006, based on a single-arm, multicenter, phase IIB study that enrolled 74 patients [76]. At a dose of 400 mg daily, the ORR was 29.7%, with a median time to response of <2 months and median duration of response of an estimated 6.1 months for stage IIB patients. A smaller phase II study (33 patients) showed very similar results (ORR 24%, median TTR 3 months, and median DOR of 3.7 months) [77]. The most common side effects included diarrhea, nausea, and fatigue. At the moment, there are no studies comparing the efficacy of different HDACi.

3.7. Combination regimens

While monotherapy is considered the best initial systemic approach when treating patients with early-stage MF, there have been suggestions that the efficacy of PUVA, IFNs, and retinoids may be increased when used in combination for treatment of advanced stage MF or refractory disease (Tables 2 and 3) [60–62,69,78–81]. In one review, however, the reported RRs to IFNα and ECP combination therapy were found to be similar to those to IFNα alone [44]. Similarly, the combination of vorinostat or gemcitabine with bexarotene did

Table 2. Selected studies of bexarotene and its combinations used in treatment of MF/SS.

Agent/s	Number of patients (*n*)	Median ORR	Median response duration	Comments
Bexarotene [58]	94	45% at 300 mg/m^2/day; 55% at >300 mg/m^2/day	299 days at 300 mg/m^2/day; 385 days for >300 mg/m^2/day	
Bexarotene [59]	58	54% at 300 mg/m^2/day; 67% at 650 mg/m^2/day	Could not be estimated for 300 mg/m^2/day dose; 516 days at 650 mg/m^2/day	
Bexarotene [82]	66	44%	8 months (range, 1–>48 months)	Twenty-eight out of 66 patients were treated with bexarotene monotherapy; the remainder were on one or more additional anti-CTCL therapies
Bexarotene + PUVA [78]	9	67%	Not stated	Median treatment duration was 4 months (range 2.5–8)
Bexarotene + PUVA [83]	46	77%	5.8 months	Forty-one patients received PUVA alone for lower ORR (71%; $p = 0.57$) but longer median duration of response (9.7 months; $p = 0.33$)
Bexarotene + vorinostat [60]	23	26%	Not stated	The average time to confirmed objective response (SWAT score) was 62 days
Bexarotene + denileukin difititox [80]	12	67%	Not stated	This was a cohort dose-escalation study with doses of bexarotene ranging from 75 to 300 mg/day
Bexarotene + methotrexate [62]	12	66%	Not stated	Six of 12 patients progressed at some point during treatment and needed additional intervention
Bexarotene + pralatrexate [84]	14	50%	Not stated	Patients received a median of 7.5 cycles (range, 2–13 cycles), with a median duration of treatment of 20 weeks (range, 4–52 weeks)
Bexarotene + gemcitabine [61]	35	31%	Not stated	Median progression free survival was 5.3 months

ORR: overall response rate; nbUVB: narrow band ultra violet B; PUVA: psoralen ultra violet A; ECP: extra corporeal photopheresis.

Table 3. Selected studies of interferon alfa and its combinations used in treatment of MF/SS.

Agent/s	Number of patients (*n*)	Median ORR	Median response duration	Comments
IFNα [85]	22	64%	Not stated (range, 2–52 weeks)	The objective response rate at the end of induction was greater for those receiving high-dose (11/14) than those receiving low-dose (3/8) therapy
IFNα [63]	24	29% (95% CI, 13–51%)	8 months (4–19 months)	No improvement in objective response was seen in the eight patients who received dose escalation
IFNα [86]	51	41% CR, 25% PR	Not stated	For patients maintained in complete remission, the mean period of response was 31 months
IFNα + PUVA [87]	39	62% CR, 28% PR	28 months (1–64 months)	
IFNα + PUVA [88]	63	75% CR, 6% PR	32 months (6–57 months)	
IFNα + PUVA vs. PUVA [89]	29	75% vs. 76% CR	Not stated	
IFNα + methotrexate [90]	158	74% CR	Not stated	Patients with refractory MF/SS were treated with low-dose MTX (<12 months) and full dose of IFN (27 MU per week)
IFNα + TSEBT vs. TSEBT [91]	41	63% vs. 36% CR	Not stated	No statistically significant difference was found in this study
IFNγ [67]	15	73.3%	Not stated	Median duration of stable disease was not reached but was >170 days (range, 29–≥253 days)
IFNα + ECP [44]	14	50%	Not stated	In responders, the time to best response was 4.3 ± 1.4 months.

IFNα: interferon alfa; IFNγ: interferon gamma; ORR: overall response rate; CR: complete remission; PR: partial remission; MTX: methotrexate; TSEBT: total skin electron beam therapy; PUVA: psoralen ultra violet A; ECP: extra corporeal photopheresis.

not improve the treatment response and was associated with increased toxicity [44].

3.8. Monoclonal antibodies (mAb) and antibody–drug conjugates

Alemtuzumab (Campath-1H) is a humanized IgG1k antibody against the CD52 glycoprotein expressed on nearly all mature leukocytes [92]. The drug was initially FDA approved for treatment of fludarabine-refractory CLL, but its use in CLL has declined with introduction of more effective and less toxic therapies. Alemtuzumab targets the central memory T cells (T_{CM}) in blood and skin of patients with SS, leading to a very effective depletion of circulating neoplastic cells (70–84% RRs) [23,93,94]. It has also been used in treatment in advanced-stage MF with less favorable responses, but it may be useful as a bridge therapy before stem cell transplant in relapsed/refractory patients. Higher dose regimens (30 mg three times a week) however are associated with an increased risk of bacterial sepsis, invasive fungal infections, CMV reactivation, and hematological toxicity [24]. Studies with lower doses (10 mg 1–2 times a week) of alemtuzumab showed excellent RRs (85–86%) with time-to-treatment failure of 12 months, and reduced risk of life-threatening infections or hematologic toxicity [22]. Alemtuzumab was withdrawn from the US market by its manufacturer on 4 September 2012 to prepare for the

planned marketing of this drug under a different name for other indications. Alemtuzumab remains accessible through a drug distribution program for the treatment of CLL and selected T-cell neoplasms, including T-cell PLL, T-cell large granular lymphocyte leukemia, and SS.

Brentuximab vedotin, an anti-CD30 antibody–drug conjugates (ADC), targets CD30+ malignant T cells in transformed MF, anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis (LyP), and Hodgkin's lymphoma (HL). After FDA's approval for relapsed HL and systemic ALCL, clinical trials have been conducted or are ongoing in CTCL patients with variable levels of CD30 expression [95,96]. A phase 2 trial in 32 patients with previously treated MF/SS reported an ORR of 70%, with responses across all levels of CD30 expression, and 54% of responders progression free at 12 months. The probability of achieving a response was lower in patients with CD30 levels of <5% [95]. Results of another phase II trial of brentuximab vedotin in the treatment of CTCL and LyP reveal an ORR of 73% and CRR of 35% [96]. Fifty-four percent of patients with MF responded, independent of CD30 expression. The ORR was 50% in patients with low CD30 expression (<10%), 58% (7/12 patients) in patients with medium CD30 expression (10–50%), and 50% (3/6 patients) in patients with high CD30 expression (≥50%). Median time to response was 12 weeks while median duration of response was 32 weeks. All patients with LyP and pcALCL responded, with similar duration of response (~26 weeks). Peripheral neuropathy, transaminitis, arthralgias, and fatigue were dose-limiting side effects [95,96]. Rare, but serious, side effects include pancreatitis, progressive multifocal leukoencephalopathy, and cytokine-release syndrome [97–99]. A randomized, phase 3 trial (ALCANZA) investigating the efficacy and safety of brentuximab vedotin versus physician's choice (methotrexate or bexarotene) in previously treated patients with CD30+ primary CTCL (MF or pcALCL) (NCT01578499) has completed accrual and first results are expected to be presented in the near future. Denileukin diftitox (DD) is FDA approved for the treatment of patients with persistent or relapsed CTCL with at least 20% CD25 positive malignant cells on skin biopsy. In a recent study of 36 patients with MF/SS, an ORR of 30.6% was achieved even in patients with low CD25 (<20%) expression [100]. The authors suggested a need for better response biomarkers for DD. The same group also reported good treatment response with DD retreatment in patients who relapsed after an initial response [101]. DD is not available at this time, but the related agent E7777 is currently being evaluated in a phase III clinical trial (NCT01871727).

Mogamulizumab (KW-0761), a humanized, fucosylated IgG1 mAb targeting the T-cell surface molecule CC chemokine receptor 4 (CCR4), shows an ORR of 36.8% and median duration of response of 10.4 months in patients of MF/SS associated with mild infusion-related side effects [102]. A phase III randomized clinical trial comparing mogamulizumab with vorinostat in patients with relapsed/refractory CTCL (NCT01728805) recently completed accrual and analysis of the data is in progress.

4. Conclusions

The role of systemic therapy in the treatment strategy of MF/SS has evolved substantially over the past 20 years, thanks to the sequential introduction of interferons, retinoids, and HDACi that combine an immune stimulatory or immune preserving effect with moderate antitumor efficacy (RR ~30 for HDACi and 45–50% for retinoids and interferons). Newer drugs, such as pralatrexate, brentuximab vedotin, and mogamulizumab are promising, but not yet approved for MF/SS in the United States, and their impact remains to be defined. Multi-agent cytotoxic chemotherapy has no role in early-stage MF and a limited role in patients with advanced stage. Single-agent chemotherapy drugs, such as liposomal doxorubicin and gemcitabine, are better tolerated than multi-agent regimens and have good efficacy in advanced stage CTCL. Numerous new agents, such as anti-KIR3DL2 IPH4102 (NCT02593045), anti-CD3 (NCT00611208) and anti-CD25 (NCT02432235) ADC, immune checkpoint inhibitors (pembrolizumab, NCT02243579), PI-3Kinase inhibitors (duvelisib, NCT02783625), and anti-microRNA 155 (MRG-106, NCT02580552) are in clinical development. While the primary goal of systemic therapy has historically been disease control in patients with advanced-stage disease, the impact on survival in this high-risk population so far has been modest, especially since drugs with moderate efficacy are used sequentially as single agents. It could be argued that the greatest impact of the currently available therapeutic arsenal in MF/SS may be in preventing stage progression in the subset of patients with skin-limited disease who are at high risk of progression to advanced stage. Considering that about two-thirds of newly diagnosed MF patients present with early-stage disease [14,16–18], identifying the genetic and immunological features that define high-risk patients and assessing the impact of therapeutic interventions in this population should be a priority in CTCL research. As we search for new therapies able to produce higher rates of complete responses, allogeneic HSCT remains the only curative option, but selecting the appropriate patients, choosing the optimal time for transplant, and balancing the risk–benefit ratio are challenges which remain to be addressed. New prognostic indices based on the recently described genomic profiling of MF/SS need to be developed to allow better selection of systemic therapy for distinct patient subsets [103–105].

5. Expert commentary

The development of a cohesive strategy for the management of CTCL focused on objective, clinically relevant, consensus-defined and broadly assessable outcome benchmarks, and aimed at achieving long-term gains, such as decreased rates of stage progression and improved survival, has long been delayed by the fact that CTCLs are rare neoplasms. Furthermore, most patients with CTCL have been traditionally managed according to single institution, expert-driven care models, which can be highly efficient but are innately biased. Most of the large outcome analyses published thus far have been based on single institution data sets, reflecting each center's different practice patterns and treatment 'philosophy.' The fact that many of the new systemic drugs used to treat CTCL are not approved outside of the United States complicates any comparison of outcome between US and non-US institutions. Collaborative international efforts to survey the global treatment landscape and define the impact of various patterns of care in CTCL have just begun.

Prospective clinical trials are still rare in CTCL. Phase II studies typically enroll less than 30–35 patients and are often underpowered. Large randomized clinical trials comparing promising, possibly more effective new therapies with relevant controls have not been published. In the absence of statistically robust, prospectively collected, outcome data, most of the retrospectively designed clinical risk stratification tools proposed to date have not been reproducible and the impact of individual variables has been difficult to confirm. One important flaw in multivariable modeling of risk, based on retrospective data, is the fact that the completeness of the data sets for specific variables is often highly inconsistent, therefore impacting the power of the analysis, and the performance of the scoring model. Another limitation is the poor reproducibility of specific risk variables among observers, in particular those based on histopathological assessment of tissue biomarkers. In the absence in centralized pathology review, immunostain-based biomarkers are unreliable.

In the arena of new drug development, the initial focus on response rates has set a relatively low bar for drug approval, which has had the welcome result of increasing the treatment options for patients, but has also left unaddressed important clinical questions, such as the impact of therapy on risk of stage progression and OS, and the comparative safety and efficacy of different agents. With drugs that – on average – produce 30–40% ORRs, mechanistic studies to address the molecular heterogeneity of the disease and develop predictive models to estimate sensitivity or resistance to individual therapies are extremely important. Future clinical trials will have to focus on these more ambitious, but essential, goals.

6. Five-year view

The accumulation and interrogation of large genomic data sets reflecting the global mutational and epigenetic landscapes of CTCL will help identifying key cancer dependencies and vulnerabilities across tumors and populations. This knowledge will guide more focused preclinical and clinical testing of existing treatment modalities in CTCL, inform the development of new combinations for systemic therapy, and lead to more personalized treatment approaches. Studies of adaptive and innate immune responses in the tumor microenvironment, together with the characterization of neo-antigen formation across distinct molecular subsets of CTCL, will lead to the optimization of existing immunotherapies and to the development of new combinatorial modalities. The routine use of high-throughput quantitative disease measurement tools, including the monitoring of minimal residual disease, will lead to better front line risk-adapted strategies and to individual tailoring of treatment duration. International collaborative efforts will come to fruition.

Key issues

- The optimal management of CTCL requires an integrated, multispeciality practice environment, with input from Dermatology, Medical Oncology, Radiation Oncology, and expert cutaneous lymphoma pathologists
- Defining and introducing reimbursement models that incentivize and reward integrated care are essential for the optimal care of these malignancies.
- Mycosis Fungoides and Sezary syndrome, the two most common types of CTCL, remain incurable lymphoid malignancies in most patients due to the lack of highly effective systemic therapies
- It is anticipated that the new 'genomics' will support the identification and validation of targets of therapy that are central to each patient's cancer vulnerabilities, therefore opening the way to truly personalized therapy.
- The lack of good risk stratification tools and accurate methodologies to measure disease burden across all anatomical compartments continues to prevent the development of a risk-adapted approach, which is essential for the design of 'intelligent' clinical trials
- The clinical efficacy endpoints that best reflect the long term impact of therapy in these chronic indolent neoplasms remain to be defined. Greater emphasis on preventing progression from early to advanced stage disease across the patient's life expectancy is necessary to increase the public health impact of treatment interventions in MF/SS
- Comparative efficacy and safety data, based on randomized clinical trials are sorely missing in CTCL. The introduction of new drugs without adequately addressing the issues of mechanism of action, tumor heterogeneity, comparative efficacy, safety, and cost will do little to drastically improve the treatment landscape in CTCL
- The development and characterization of robust animal models of CTCL that are relevant for drug development and pharmacodynamics studies, and reproduce many if not all aspects of human disease should be a priority.
- Multi-agent cytotoxic chemotherapy is significantly inferior to immune-stimulating or immune-sparing therapies. Continued emphasis should be placed in understanding and leveraging the host immune system for long term disease control.

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