Mycosis fungoides and Sezary syndrome – Simplifying the approach for dermatologists. Part 2: Evaluation, staging, prognosis and treatment

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Abstract

Cutaneous T-cell lymphoma is a heterogeneous group of T-cell neoplasms, of which mycosis fungoides and Sezary syndrome are the most common. The prognosis depends on the stage of the disease. The early stage follows a protracted course with a five-year disease-specific survival of greater than 95% and is treated with skin-directed topical therapies, phototherapy, and oral drugs like methotrexate. Advanced disease has a five-year overall survival of less than 25% and requires management by systemic chemotherapeutic agents. This review article is the second part out of the two covering the staging, prognosis, and treatment from a dermatologist's perspective.

Key words: Mycosis fungoides, Sezary syndrome, CTCL, cutaneous T cell lymphoma

Introduction

A thorough clinical assessment and evaluation helps to stage the disease which helps determine the prognosis of the patient. The staging also helps clinicians to decide the drug therapy. In this article, we go through the pointers in clinical examination and evaluation, which help determine the staging and prognosis with treatment implications.

Staging and prognosis

The factors affecting the staging of Cutaneous T-cell lymphoma (CTCL) depend on numerous factors from the morphology and extent of the skin tumour to histopathology and imaging findings. The most common type of CTCL, that is, mycosis fungoides and Sezary syndrome (MF/SS) are classified into stages IA through IVB using the tumour, lymph node, metastasis, and blood involvement (TNMB) system [Table 1]. Stages up to IIA are early-stage diseases and can be managed by dermatologists alone. Stages IIB through IVB are considered advanced stage disease and should be managed in consultation with oncologists [Table 2].

Clinical findings and their prognostic significance

The extent of body surface area involvement and lesional morphology has a direct bearing on the staging of the patient. Involvement of the head and neck area, as seen in folliculotropic MF, is a poor prognostic factor. Since the pathology involves the perifollicular areas, it is anatomically

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Table 1: ISCL/EORTC revision to the classification and staging of MF and SS

TNMB Classification	Characteristics
Tumour (T)	
T1	Limited patches, papules and/or plaques covering <10% of the skin surface; may further stratify into T1a (patch only) versus T1b (plaque +/– patch)
T2	Patches, papules or plaques covering ≥10% of the skin surface; may further stratify into T2a (patch only) versus T2b (plaque +/– patch)
T3	One or more tumors (≥1 cm diameter
T4	Confluence of erythema covering ≥80% body surface area
Node (N)	
N0	No clinically abnormal peripheral lymph nodes; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2
N1a	Clone negative
N1b	Clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative
N2b	Clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Metastasis (M)	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood (B)	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells
B0a	Clone negative
B0b	Clone positive
B1	Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumour burden: ≥1000/μL Sezary cells with positive clone

Table 2: ISCL/EORTC revision to the staging of mycosis fungoides and Sezary syndrome with five-year disease-specific survival (DSS)

Stages of MF	T	N	M	B	Prognosis (DSS at five years)
IA	1	0	0	0-1	100%
IB	2	0	0	0-1	95%
IIA	1-2	1-2	0	0-1	84%
IIB	3	0-2	0	0-1	56%
III	4	0-2	0	0-1	65%
IIIA	4	0-2	0	0	65%
IIIB	4	0-2	0	1	65%
IVA_1	1-4	0-2	0	2	30%
IVA_2	1-4	3	0	0-2	30%
IVB	1-4	0-3	1	0-2	30%

T- Tumour, N- Node, M- Metastasis, B-Blood involvement.

deeper than classical MF and translates to a poor five-year survival rate than the expected clinical stage.[1,2]

The presence of even a single nodule is another independent prognostic marker and suggests a poor prognosis. In fact, in case if a particular patient has a nodule in addition to erythroderma, it is advised to record the patient as $T_{4(3)}$ to cover for the impact of the presence of even a single nodule in erythroderma.[3]

Any new onset nodule or an ulcer may also suggest a large cell transformation (LCT) which translates into a poor five-year survival rate. LCT is diagnosed when a skin biopsy shows large cells (≥4 times the size of a lymphocyte) in 25% or more of the dermal infiltrate or a specimen that demonstrates large cells in nodules.[4] To support this particular diagnosis, CD30 should be performed, although this positivity may be found in malignant disease like primary cutaneous CD30+ anaplastic large cell lymphoma and benign disease like lymphomatoid papulosis as well.

SS too has a poor prognosis with similar ten-year survival rates as stage IV of MF.[5] It is important to distinguish erythrodermic MF and SS, as they are distinct nosologic entities having different disease characteristics in terms of etiopathogenesis, clinical characteristics, and prognosis. The World Health Organisation and the European Organisation for Research and Treatment of Cancer (WHO/EORTC) consider SS to be a triad of erythroderma, lymphadenopathy, and leukaemic disease. Erythrodermic MF presents with generalised erythema accompanied by scaling, which may or may not be associated with clinical and/or histopathological involvement of lymph nodes. But as a rule, leukaemia is never seen. However, rarely a case of MF with classical skin

lesions may progress to erythrodermic MF and subsequently lymphadenopathy accompanied by abnormal blood picture which are referred to as SS preceded by MF, leukaemic MF, or secondary SS. It is pertinent to remember that almost all cases of SS are de novo or primary which do not present with an antecedent history of MF and secondary SS is exceedingly rare.

Identification of abnormal lymph nodes not only helps correlate the histopathology and immunohistochemistry findings with that of the skin but also stages the disease which will ultimately decide the choice of therapy. In a study on the frequency and stage of lymph node involvement in 24 patients of MF, approximately a quarter had histological findings of dermatopathic lymphadenopathy (stage 1); a third were in stage 2 (early involvement of lymph nodes); and around 10% were in stage 3 and 4 each (partial and complete effacement, respectively).[6] A fine needle aspiration cytology (FNAC) is insufficient since it cannot determine the above mentioned spectrum of changes affecting the lymph node architecture. As of now, the central lymph nodes like intra-abdominal, intrathoracic, and intrapelvic lymph nodes are excluded from tumour, node, and metastasis (TNM) classification, except for a scenario where a biopsy has been done of these nodes to prove lymphomatous involvement, which is difficult as well as rarely performed.

The presence of hepatomegaly should arouse suspicion of metastasis. Consistent with the Cotswolds meeting on Hodgkin lymphoma, the presence of multiple focal hepatic defects, which are neither cystic nor vascular, on at least two imaging techniques may be considered indicative of tumour involvement.[7] Abnormal liver function tests or radiologic tests like computed tomography or/and fluorodeoxyglucose-positron emission tomography (CT or/and FDG-PET) should be confirmed by liver biopsy.[8] Similarly, histopathological examination of the lungs is necessary before diagnosing any pulmonary radiological abnormalities as metastasis. The International Society for Cutaneous Lymphomas (ISCL) and EORTC consider splenomegaly as visceral disease, even without biopsy confirmation, when it is (a) unequivocally present on physical exam and (b) documented radiographically by either enlargement or multiple focal defects that are neither cystic nor vascular.[8]

One of the problems with applying TNMB staging is that it ignores the percentage body of surface area involvement, except when it is distinguishing between the a and b stages of T1 and T2. Also, it is difficult to assess the outcome of a particular therapy using the current TNMB classification. Modified Severity-Weighted Assessment Tool (mSWAT) uses a continuous scale like that of the Eczema Area and Severity Index (EASI) and Psoriasis Area and Severity Index (PASI), facilitating a precise assessment of the area of skin involvement by type of lesion. With mSWAT, it is possible to assign patients a numerical value for assessing treatment responses/outcomes, for comparative studies and for monitoring clinical trials in a quantitative manner [Table 3].

Based on the variables and scoring, a prognostic index called the cutaneous lymphoma international prognostic index (CLIPI) has been designed for MF/SS.[9] Significant adverse prognostic factors at diagnosis consists of male gender, age >60 years, plaques, folliculotropic disease, and stage N1/Nx for early stage; stages B1/B2, N2/3, and visceral involvement for late- stage disease. The patients are classified into three groups for early (IA–IIA) and late stages (IIB–IVB): 0–1 (low risk), 2 (intermediate risk), and 3–5 factors (high risk).[9] A ten-year overall survival (OS) in the early-stage model was 90.3% (low), 76.2% (intermediate), and 48.9% (high), and for the late-stage model 53.2% (low), 19.8% (intermediate), and 15.0% (high).[9] A summary of prognostic factors is tabulated in Table 4.

Treatment

Treatment recommendations for MF/SS by disease stage recommended by EORTC (2023) are very well elucidated in the review article by Latzka *et al*.[10] The management is aimed at complete remission (CR). Stages up to IIA are 'early stage' and can be managed by dermatologists independently. Stages from IIB are 'advanced stage' and should be managed by a team consisting of dermatologists with clinical and radiation oncologists. Stage-wise choices of treatment modalities are enumerated in Table 5.

Table 3: Assessment of response using mSWAT (modified severity-weighted assessment tool)

Response	Definition
Complete response	100% clearance of skin lesions
Partial response	50%–99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease	≥25% increase in skin disease from baseline or new tumours (T_3) in patients with T_1, T_2 or T_4 only skin disease or loss of response in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

Table 4: Poor prognostic factors in MF and SS

Variable	Poor Prognosis
Age*	More than 60 years
Gender*	Male
Body surface area (BSA) involvement	More the BSA involved, worse is the prognosis (T2b > T2a)
Type of skin lesions*	Thick plaques, nodules
Folliculotropism*	Folliculotropism present
Course	New onset nodules, ulceration
Cell morphology	Large cell transformation (presence of CD30− or CD30+ large cells (at least four times larger than a small lymphocyte) exceeding 25% of the infiltrate or forming microscopic nodules)
Lymph node*	Lymph node involvement
Histopathology of lymph nodes	Higher the grade, worse the prognosis
Metastasis*	Early metastasis
Hematopoietic system (blood)/Sezary syndrome*	Absolute Sezary cell count of >1000/μL or an expanded $CD4^+$ T-cell population resulting in a CD4/CD8 ratio ≥10, $CD4^+/CD7^-$ cells ≥40% or $CD4^+/CD26^-$ cells ≥30%)
Serum lactate dehydrogenase (LDH)	High Lactate dehydrogenase
T-cell clonality	Present

The variables marked (*) are included in CLIPi (Cutaneous Lymphoma International Prognostic index).

Expectant policy (wait and watch): Stage IA disease has a low risk of progression, which has been projected to be 10% in a decade, with similar life expectancy as that of age- and sex-matched population.[11] Hence 'wait and watch' is a legitimate management option for patients in MF stage IA. But this approach should include periodic monitoring and patient education, so as to follow up the fraction of patients who will eventually progress to advanced stages.

Skin-directed therapies

Topical steroids: The first-line treatment for early-stage MF is mid-potent to super-potent topical steroids with an overall response rate (ORR) of 94% in the T1 stage and is associated with minimal to no toxicity.[12]

Nitrogen mustard/Chlormethine 0.02% gel: Chlormethine gel is recommended as first-line treatment of early-stage disease (stages IA to IIA) which has an ORR of 93% in the T1 stage.[13] Since there are no evidence of systemic absorption of topical nitrogen mustard, systemic adverse effects have not been reported.[14] Chlormethine gel is a ready-to-use formulation but may not be available all across the globe. Alternatively, mechlorethamine hydrochloride 10 mg powder is available in sterile glass vials. To prepare the desired concentration of aqueous solution for direct application on the skin, a small amount of tap water (2–3 mL) is added into the glass vial using a syringe to dissolve the powder. The dissolved solution is then withdrawn and added to prepare a total volume of 100 ml.[15] After performing a patch test for contact dermatitis, it is then applied on to the skin using either a sponge or cloth. The aqueous preparation is unstable and must be used immediately after reconstitution. Both gel and reconstituted solution are used once daily. The most common adverse effect is allergic or irritant contact dermatitis reported in over 50% of patients resulting in withdrawal in approximately one-fifth of the patients.[16] A study has suggested better clinical response in patients developing contact dermatitis.[17] Hence, rather than completely withdrawing this therapy, the irritant contact dermatitis is managed by treatment interruption and reintroduction with longer intervals between applications and by combination with topical corticosteroids.

Carmustine (BCNU): Carmustine (BCNU) is a nitrosourea alkylating agent which is used as topical therapy in early stages of MF. It is available as 100 mg lyophilized powder in a vial. It is dissolved by injecting 5 mL of 95% ethanol with a syringe. The 5 mL is then withdrawn and put in a larger glass container and diluted to 50 mL with 95% ethanol to prepare a stock solution of 2 mg/mL (0.2%). It is stable (2–8°C) for at least three months. For total body applications, 5 mL (10 mg BCNU) of the 0.2% stock solution is diluted in 60 mL tap water.[18] The volume of solution is adjusted to the area of skin involved. The applications are done at a once daily frequency. For limited skin involvement, undiluted stock solution may be applied using a cotton tipped applicator. A personal protective kit is advised for personnel reconstituting as well as administering BCNU, as it is a potential carcinogen.

Bexarotene 1% gel: It is Food and Drug Administration (FDA) approved for topical treatment of cutaneous lesions in patients stage IA and IB who are refractory to or have not tolerated other therapies. Prospective trials have demonstrated an ORR between 44% and 63%.[19] It is applied once daily to the affected areas. Adverse effects include mild irritation of skin and teratogenicity and are hence contraindicated in pregnancy.

Others: Topical calcineurin inhibitors (tacrolimus, pimecrolimus)[20,21] and Toll-Like Receptor agonists (imiquimod, resiquimod)[22,23] have also been tried in small studies with some success.

Phototherapy

Narrow Band Ultra Violet B (NBUVB), broad band UVB (BBUVB), excimer laser, and Psoralen plus Ultra Violet

Table 5: Stage-wise treatment approaches for mycosis fungoides and Sezary syndrome

First line	Second line
Recommendations for management of MF stages IA, IB and IIA	
Expectant policy (mainly IA)	Systemic therapies
Topical corticosteroids (mainly T1a and T2a)	Retinoids
Topical chlormethine	IFNα
NBUVB (mainly T1a and T2a)	TSEBT (mainly T2b)
PUVA	Brentuximab vedotin
Localised radiotherapy (for localised MF, including pagetoid reticulosis)	Mogamulizumab
	Low dose methotrexate
Recommendations for management of MF stages IIB	
Retinoids	(Poly-) chemotherapy
IFNα	Brentuximab vedotin
TSEBT	Mogamulizumab
Brentuximab vedotin	Allogeneic stem cell transplantation
Mogamulizumab	
Monochemotherapy (pegylated liposomal doxorubicin, gemcitabine, pegylated liposomal doxorubicin)	
Low dose methotrexate	
Localised radiotherapy	
Recommendations for management of stage IIIA and B	
Retinoids	Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)
IFNα	Brentuximab vedotin
ECP	Mogamulizumab
Brentuximab vedotin	Allogeneic stem cell transplantation
Mogamulizumab	
Low dose methotrexate	
TSEBT	
Recommendations for management of stage IVA and B	
Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)	
Radiotherapy (TSEB and localised)	
Brentuximab vedotin	
Mogamulizumab	
Alemtuzumab (mainly in B2)	
Allogeneic stem cell transplantation	
Recommendations for management of SS	
ECP	Mogamulizumab
Systemic therapies in combination with ECP or PUVA	Brentuximab vedotin
Retinoids	Alemtuzumab
IFNα	Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)
Chlorambucil + prednisone	
Low dose methotrexate	Allogeneic stem cell transplantation

Abbreviations: IFNα: Interferon α; TSEBT: Total Skin Electron Beam Therapy; ECP: Extra Corporeal Photopheresis; PUVA: Psoralen plus Ultra Violet A; CHOP: Cyclophosphamide, Doxorubicin, Vincristine(Oncovin) and Prednisolone

A (PUVA) constitute first-line therapies in early-stage MF, especially in those with suboptimal response to topical therapy alone. In a meta analysis comprising of 778 patients, higher complete response (73.8%) was found in patients who received PUVA as compared to that of NBUVB (62.2%) which was statistically significant. (P=.04).[24] The higher response rate in the former is due to the longer wavelength of PUVA enabling deeper penetration in the skin, especially in the presence of the plaque stage of MF. Although completion rate (CR) is lower in NBUVB, it still may be considered as the first line therapy for early stage MF. PUVA may be considered as first-line therapy but should be reserved in those with patches/plaques unresponsive to NBUVB because oral psoralen is associated with adverse effects like nausea, vomiting and phototoxicity, and skin cancers in the long term. Targeted phototherapy like excimer laser is preferred in localized patch/plaque stage.[25] Phototherapy is administered in twice or thrice weekly sessions till CR and then maintained once weekly to once monthly or even fewer sessions. The phototherapy sessions may be continued as per schedule until disease remission, followed by maintenance therapy to extend the disease-free period.[26]

Total skin electron beam therapy

Total skin electron beam therapy (TSEBT) is generally indicated for the tumour (T3) or erythroderma (T4) stage, and can also be used for stage T2 not responding to first-line treatments. Neoplastic cells in MF are relatively radio-sensitive. Radiotherapy provides further advantage of delivery to any extent of body surface area with increased penetration into the deeper layers of skin when compared to skin-directed topical therapies. The principle of TSEBT is

based on the fact that there is a rapid dose fall-off, which limits penetration of electrons to deeper tissues like internal organs, including the bone marrow, limiting toxicity. The treatment protocol is administered by rotational or 'six-field' technique in a standing position. To be able to induce high remission rates, the conventional TSEBT regimen is administered two to four days a week over a period of eight to ten weeks to a total of 30–36 Gy.[27] The most common acute adverse effects of TSEBT are erythema, skin pain, desquamation, blistering, postinflammatory hyperpigmentation, shedding of nails, and hypo- or anhidrosis resulting in chronic xerosis and potentially irreversible alopecia. The initial response may be successfully sustained by follow-up maintenance sessions without significant additional toxicity. For even better efficacy, TSEBT can be combined with nodal and localized skin irradiation. To limit the toxicity, low doses (10–12 Gy) as well as short-duration regimens (two to three weeks) have been tried.[28,29] A study comparing low dose TSEBT to conventional TSEBT found that the former had an ORR of 85%, mild adverse events rate of 93%, and severe adverse events rate of 5%, whereas conventional TSEBT had an ORR of 99%, mild adverse events at 100% and severe adverse events rate at 7%.[30] TSEBT requires a linear accelerator and is technically demanding to administer, and hence is available only in bigger centers.

Systemic therapy

Low dose methotrexate: Low-dose methotrexate is indicated in patients showing suboptimal response to topical therapies or phototherapy. In a retrospective study in 69 patients, low-dose oral methotrexate resulted in ORR of 33% and 58% in patch/plaque MF and erythrodermic MF, respectively.[31] Doses ranging from 10 mg per week to 75 mg per week have been used. Common side effects are nausea, vomiting, loss of appetite, oral mucositis, and myelosuppression.

Bexarotene: Owing to its specific binding to the retinoid-X-receptor (RXR), it is the only member of the oral retinoid group that has been specifically developed and given approval for the management of CTCL. Bexarotene is indicated for the treatment of advanced-stage CTCL in patients who are refractory to at least one prior systemic therapy with an ORR of 45%. It is available as 75 mg capsules and is given once daily after a meal at a dose of 300 mg/m^2/day, and may be reduced to 100–200 mg/m^2/day as tolerated. It may be continued for as long as the patient derives benefit. Hyperlipidemia, hypertriglyceridemia, and hypothyroidism are very commonly seen (roughly up to 50% of patients). Other adverse effects are xerosis, dryness of mouth and mucous membranes, leukopenia, cataract, and photosensitivity. It is a teratogen and hence a pregnancy category X drug. In a randomised controlled trial (RCT) in 87 patients, which compared psoralen + ultra violet A (PUVA) plus bexarotene versus PUVA alone, it found no statistical superiority of the combination than that of PUVA, but there was a trend towards fewer PUVA sessions (median 22 versus 27.5, p = 0.11) and lower ultra violet A (UVA) (median 55.8 J/cm^2 versus 117.5 J/cm^2, p = 0.5) dose required to achieve complete clinical response in the combination arm.[32]

Pegylated Interferon alpha (PEG-IFNα): IFNαs have antiviral, anti-tumour, immunomodulatory, and antiproliferative properties. IFNα is being replaced with that of its pegylated form, since the latter possesses a longer half-life in plasma due to reduced renal clearance, and is now being increasingly used in CTCL. As compared to conventional IFNα which was administered thrice weekly, the pegylated form is given once a week. The most commonly used regimen for standard IFNα is to start with three million units (MU) subcutaneously thrice weekly, with dose escalation usually up to 10 MU, but have been used up to 18 MU upon insufficient response. The PEG-IFNα is administered at 1.5 µg/kg/week, but doses up to 360 µg per week have been given.[33] A retrospective cohort study in 31 MF patients was held across all stages on PEG-IFNα 2a alone or in combination with bexarotene, acitretin, methotrexate, and topical chemotherapy reported an ORR of 54.8% (CR 9.7%, PR 45.2%).[34] Adverse effects are dose-dependent and include flu-like symptoms, leukopenia, thrombocytopenia, elevated transaminases, depression, suicidal ideation, cardiac arrhythmias, blurring of vision, retinal defects, optic neuritis, and thyroid dysfunction. IFNα is mostly combined with either phototherapy, total skin electron beam theray (TSEBT), or with systemic retinoids for better efficacy.

Other systemic therapies in advanced stages

The authors briefly touch upon the available chemotherapeutic options and recent advances as well as those on the horizon. Almost all of them are beyond the purview of dermatologists as they are mostly likely to be used by oncologists.

Chemotherapy: Combination chemotherapy consisting of Cyclophosphamide-Hydroxydaunorubicin-Oncovin-Prednisolone (CHOP) regimen is an option exercised by oncologists in aggressive CTCL or SS till recent past. Etoposide, Prednisolone, Oncovin, Cyclophosphamide-Hydroxydaunorubicin (EPOCH) may be administered in refractory lymphomas.[35] With the advent of newer yet safer chemotherapeutic agents, more cases are being treated with monochemotherapy with agents like pegylated liposomal doxorubicin and gemcitabine.[36–38]

Targeted Immunotherapy: Denileukin diftitox is a genetically engineered recombinant protein consisting of interleukin (IL)-2 linked to the catalytic domain of diphtheria toxin; this was developed as a treatment option for CTCL and became the first fusion toxin to be approved.[39] A couple of phase III trials demonstrated ORRs of 30% and 44% with an acceptable safety profile. However it is currently unavailable and hence has been left out of EORTC recommendations.[40,41]

Alemtuzumab is a monoclonal antibody against the CD52, which is expressed on normal as well as malignant T and B lymphocytes but not on their haematopoietic progenitors.

ORR of 50% have been achieved in MF/SS using the standard dose of 30 mg intravenous thrice weekly.[42] It is a promising drug for long-term remission in T4 and B >1 stage disease. Since it inhibits both T as well as B cells, gross immunosuppression leading to opportunistic infections are most commonly seen at this dosage.[42] With the intention to maintain efficacy and reduce toxicity, low dose regimen (10–15 mg instead of 30 mg) have been introduced, leading to similar efficacy and avoiding opportunistic infections.[43]

Brentuximab vedotin is an antibody drug conjugate consisting of an anti-CD30 IgG1 antibody moiety attached to monomethyl auristatin E targeted against CD30 molecule. Although not included in the EORTC recommendations, it may be tried on a case-to-case basis in advanced CD30+ cases.[44]

Mogamulizumab is a monoclonal antibody against the CC chemokine receptor 4 (CCR4) expressed on tumour cells of many T-cell lymphomas. The drug is approved in Japan for relapsed or refractory CCR4+ peripheral T-cell lymphoma and CTCL. Although the data for this drug is sparse, it has shown promise in leukaemic variant with an ORR between 38% and 29%.[45,46]

Histone deacetylase inhibitors (HDACi): Three drugs of this class have received FDA clearance for CTCL or peripheral T-cell lymphoma (PCTL) – vorinostat, romidepsin and belinostat. They have reported an ORR of about 30%.[47]

Extracorporeal photochemotherapy (ECP): Also known as extracorporeal photoimmunotherapy, extracorporeal photopheresis or simply photopheresis, this is a type of phototherapy where the leukocyte-enriched fraction of blood spiked with 8-methoxypsoralen (8-MOP) is exposed to a UVA light source extracorporeally and then returned to patients. It received FDA approval in 1988 for CTCL. It is especially preferred in B2 stage (leukaemic variant of CTCL; SS) or in T4 (erythroderma) with ORR varying from 33% to 74%.[48,49] A typical regime consists of a session on two consecutive days every four weeks. ECP, when combined with IFN-α or bexarotene, has shown to have better response rates than either of them alone.[50]

Haematopoietic stem cell transplantation: Allogenic stem cell transplantation is able to achieve long-term remissions in MF/SS, but with high rate of treatment-related mortality and morbidity. It requires careful patient selection and counselling, targeting younger patients in advanced stages of the disease, albeit with a high predictable risk of progression and poor prognosis but low tumour burden at the time of transplantation.[51]

The individual as well as combination of various topical as well as systemic treatment options with their levels of evidence are summarised in the supplementary table 1.[52]

Conclusion

Early MF usually has an indolent course, but a proportion of patients progress to advanced stages over time. Prognostic tools like CLIPi have been developed to identify patients at risk of progression and poor outcome. Early MF is generally treated with a conservative skin-directed approach: topicals and light therapy. Systemic therapies are largely reserved for advanced stages of MF; single-agent chemotherapy and biological response modifiers are preferred over multiagent chemotherapy.

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