

Proposal of a comprehensive model for palliative therapeutic interventions in patients with mycosis fungoides and Sézary syndrome

Propuesta de modelo integral para intervenciones terapéuticas paliativas en pacientes con micosis fungoide y síndrome de Sézary

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Abstract

This paper provides information on the generalities of cutaneous T lymphomas, and the alternatives of targeted and palliative management based on the scales currently available in a medical literature search in patients with mycosis fungoides and Sézary syndrome (MF/SS). This was a narrative review of the medical literature available with MeSH terms conducted in databases such as PubMed, Google Scholar, Embase and Web of Science, with no time limit. There are multiple factors that should be considered regarding the quality of life of patients with cutaneous T-cell lymphomas even at the early stages of the disease. Therefore, a comprehensive model of palliative therapeutic interventions for patients with MF/SS is proposed. Palliative therapeutic management in patients with MF/SS should be understood in a biological, psychosocial, and emotional context as part of a comprehensive and multidisciplinary intervention to improve the quality of life of this population.

Keywords: Sézary syndrome. Mycosis fungoides. Quality of life. Palliative care.

Resumen

El documento ofrece la información recolectada acerca de las generalidades de los linfomas T cutáneos, así como las alternativas de manejo, tanto dirigido como paliativo, basadas en las escalas disponibles de búsqueda de la literatura en pacientes con micosis fungoide (MF) y síndrome de Sézary (SS). Se realiza una revisión narrativa de la literatura con términos MeSH en bases de datos como PubMed, Google Scholar, Embase y Web of Science, sin límite de tiempo. Existen múltiples factores a tener en cuenta en la calidad de vida de los pacientes que se presentan inclusive desde estadios tempranos de los linfomas T cutáneos, por lo que se propone un modelo integral de las intervenciones terapéuticas paliativas de los pacientes con MF/SS. El manejo terapéutico paliativo en pacientes con MF/SS se debe comprender en un modelo biológico, psicosocial y emocional, lo que permite una intervención integral y multidisciplinaria, buscando mejorar la calidad de vida de la población mencionada.

Palabras clave: Síndrome de Sézary. Micosis fungoide. Calidad de vida. Cuidados paliativos.

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Introduction

Mycosis fungoides (MF) and Sézary syndrome (SS) have limited curative options, so treatments are predominantly palliative. Therefore, treatment should try to minimize symptoms and improve the patients' quality of life. However, the guidelines on the management of cutaneous T-cell lymphomas (CTCL) do not include specific recommendations on the supportive care needs of patients and their families or caregivers. That is why a multidisciplinary evaluation and management approach focused on both physical and psychosocial functioning is necessary to enhance the quality of care provided to patients and their caregivers¹⁻³. The primary endpoint is to propose a comprehensive model of palliative care for patients with MF/SS to improve their quality of life. Secondary endpoints are to review the information described in databases on therapeutic interventions in patients with MF/SS and update the factors impacting the quality of life of these patients.

Method

This was a narrative review after a literature search in PubMed, Google Scholar, Embase, and Web of Science databases without a time limit. The search included keywords such as "mycosis fungoides", "Sézary syndrome", "quality of life", and "multidisciplinary management". The inclusion criteria were the following: adult human population found in any type of publication such as original research or panoramic, systematic, or meta-analysis reviews. Animal studies, other health conditions different from MF/SS, editorial publications, letters, comments, books or book chapters, congress records or abstracts were excluded. Articles without abstracts and those in languages other than English or Spanish were also excluded. The PubMed search was conducted as follows: Mycosis Fungoides AND Sézary Syndrome AND quality of life[MeSH Terms]. ((dignity therapy intervention) AND (mycosis fungoides [MeSH Terms])) AND (lymphoma, Sézary's[MeSH Terms]).

Results

MF and SS, included in the CTCL group, are the 2 most common presentations within this heterogeneous group. Both are rare diseases that tend to be chronic and relapsing, with visible and potentially disfiguring and disabling skin lesions. These conditions can be associated with alopecia and varying cutaneous

symptoms such as scaly rash, itching, burning, and sometimes even pain^{4,5}.

Summary of the evidence available

CTCL include a group of mature T-cell neoplasms with different phenotypic characteristics determining the prognosis of each condition. These neoplasms are different from the neoplasms of T-cells and natural killer (NK) cells, a distinction that will most definitely guide the prognosis of each condition. According to the classification established by the World Health Organization (WHO) in 2016, CTCL can exhibit aggressive behaviors or indolent courses^{3,6,7}.

The diagnosis of a primary cutaneous lymphoma is based on clinical, histopathological, immunophenotypic, and genotypic findings of the lesions, as well as in the presence of extracutaneous involvement. Approximately 75% of the cases have a T-cell phenotype, while two-thirds are MF/SS, that is, these 2 conditions are the most common ones^{8,9}. MF and SS are considered chronic and incurable diseases. In their early stages (patches or plaques), treatment is limited to skin interventions, and as disease progresses, systemic treatment becomes necessary.

MF typically presents with patches or plaques that often have a "bathing suit" distribution and are pruritic in nature. Patients initially experience patch/plaque disease (stage I, affecting < 10% of the skin surface), and up to 20% may have lymph node involvement. Because this disease cannot be cured and early therapies do not impact survival, a non-aggressive approach is advised².

SS represents the advanced stage of the disease, and is characterized by erythroderma, generalized lymphadenopathies, and presence of Sézary cells in the skin, lymph nodes, and peripheral blood. It is associated with an aggressive course with 5-year overall survival rates of 20% to 30%, with lower rates based on Sézary cell count¹⁰⁻¹². The symptoms of MF/SS are multidimensional and listed in [table 1](#).

EPIDEMIOLOGY

MF accounts for up to 60% of all cases of CTCL, with varying clinical presentations ranging from localized patches and plaques to ulcerative tumors or erythroderma with extracutaneous involvement.

SS is a rare and aggressive leukemic type of CTCL, with an estimated incidence of 0.075 cases per 100 000 people. SS is defined by the triad erythroderma,

Table 1. Summary of the most common symptoms categorized by domain

Domain	Symptoms
Physical	Weakness Pain Treatment-related side effects such as neuropathy, nausea, and vomiting Night sweats, fever Itching Weight loss Loss of appetite
Social	Social distancing Disease acceptance Sexual satisfaction
Emotional	Sadness Hopelessness Anxiety Preoccupation on disease progression Frustration Shame
Functional	Removal of working activity Anhedonia Sleep disorder Altered quality of life

lymphadenopathy, and blood involvement². The median survival of patients with MF with generalized patches or plaques (T2 according to the WHO classification) is 11.7 years. At this stage, 24% may progress into a more advanced clinical stage, and approximately 20% will eventually die from the disease. In advanced MF (stages IIB to IV: tumors and erythroderma), the median overall survival is 63 months, with 2- and 5-year survival rates of 77% and 52%, respectively^{13,14}.

FACTORS LEADING TO POOR PROGNOSIS

Quality of life is negatively influenced in all subtypes of cutaneous lymphomas, but quality of life is particularly impacted in patients with MF/SS, particularly patients with follicular MF. Multiple factors such as the lack of categorization of lesion size or the percentage of affected body surface area, disease burden, or lesion locations (eg, facial involvement) lead to contrasting results that may contribute to this impact. Other established factors associated with a lower quality of life include female sex, young age, black race, and advanced stages of MF/SS¹⁵.

Racial/ethnic disparities in quality of life have been reported by different studies, being the quality of life of black patients worse than that of white patients, even after controlling for the confounding factors¹⁶.

TREATMENT

The following are treatment recommendations from the International Society for Cutaneous Lymphomas, the U.S. Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organization for Research and Treatment of Cancer:

- Patients with stage IA disease can be managed expectantly with careful monitoring. If treatment is required, options include topical steroids, topical nitrogen mustard, total skin electron beam radiation therapy, and cutaneous phototherapy via oral administration (typically using psoralen plus UV A radiation). Low-dose radiation may be useful for symptom improvement and esthetics^{14,17}.
- Spread disease can be properly treated with methotrexate or corticosteroids, although responses are often short-lived. Single-agent treatments are preferred, especially in slow-progressing disease, due to the high risk of myelosuppression and infection and the duration of response. In the presence of disease progression alternatives include interferon alpha, bexarotene, vorinostat, romidepsin, and brentuximab vedotin, all with demonstrated efficacy to treat advanced MF and SS¹⁸⁻²².
- Allogeneic transplantation has been explored in selected cases of MF and SS. The European Group for Blood and Marrow Transplantation reported on a multicenter, retrospective study that evaluated allogeneic transplantation (myeloablative and reduced-intensity conditioning [RIC] regimens) in 60 patients with MF (n = 36) or SS (n = 24). In almost half of the population, refractory disease was documented at the time of allogeneic transplantation, with higher survival rates in the RIC group^{21,22}.

ADVANCED STAGES

Large cell transformation in MF is defined as large cells in over 25% of the infiltrate or as cells forming microscopic nodules. The incidence rate ranges from 8% to 39% and it often has a grim prognosis, although some long-term survivors have been described. Factors associated with lower specific disease survival include CD30-negative status, folliculotropic MF, generalized cutaneous lesions, and extracutaneous transformation. Cases without risk factors had a 2-year disease-specific survival rate of 83% compared to the 14% to 33% reported in patients with 3 or 4 risk factors. The optimal management is not clear here, but for young patients, systemic chemotherapy should be used, and autologous

Table 2. General and specific cutaneous T lymphoma-related multidimensional scales

Cutaneous T lymphoma-related general multidimensional scales	Dermatology	Modified Severity-Weighted Assessment Tool (mSWAT) ^{25,30} , Skindex-29/16 ³⁹ , Dermatology Life Quality Index (DLQI), Dermatology Life Quality Index ⁴⁰
	General tools for symptoms and specific perception	Itchy Quality of Life (ItchyQoL) ⁴¹ , Pruritus ENA ⁴² , <i>Pruritus-5D itch scale</i> (5D) ⁴³ , <i>Revised Illness Perception Questionnaire</i> (IPQ-R) ⁴⁴
	Cancer related	<i>Functional Assessment of Cancer Therapy</i> (FACT-G), FACT-lym ³⁶ , Spitzer ⁴⁵ , <i>Core Quality of Life Questionnaire</i> (QLQ-C30) ⁴⁶
	Emotional symptoms	<i>Inventario de la dignidad del paciente</i> ³³ , <i>Beck Depression Inventory</i> (BDI), <i>Beck Anxiety Inventory</i> (BAI) ⁴⁷
	Symptoms associated with sexual dysfunction	<i>The PROMIS Sexual Function and Satisfaction</i> (SexFS) ³⁷
Cutaneous T lymphoma-related specific multidimensional scales	<i>Cutaneous Lymphoma Distress Questionnaire</i> (CL-DQ), <i>Mycosis Fungoides/Sézary Syndrome-Cutaneous T-Cell Lymphoma Quality of Life</i> (MF/SS-CTCL QoL)	

or allogeneic transplantation should be considered, especially for high-risk disease. Consolidative radiation can be an option for local transformations^{6,21,23}.

The treatment is based on 2 different scenarios: patients without large cell transformation involvement or with skin involvement only, and patients with extensive large cell transformation or aggressive skin clinical involvement. All stages require treatment for symptomatic control, such as skin-directed therapy, antipruritic agents, external beam radiation, and total skin electron beam therapy.

Patients without extensive large cell transformation involvement or skin disease only, treatment may receive radiation therapy, single-agent therapy, and targeted skin therapy. Allogeneic hematopoietic stem cell transplantation may be considered as well. Patients with extensive large cell transformation involvement or aggressive clinical skin involvement may receive combination therapy. Autologous hematopoietic stem cell transplantation can be an option for patients with complete responses, and allogeneic transplantation in patients without complete responses (young patients, aggressive clinical disease, or after exhausting other options)^{23,24}.

Multidisciplinary palliative management

The primary goal of palliative care is to provide symptomatic relief and address the patient's needs comprehensively.

In the medical literature available, the most predominant and distressing symptom often reported is pruritus (itching). Neurokinin antagonists, such as aprepitant,

are the most effective antipruritic agents, providing adequate control of chronic pruritus (lasting more than 6 weeks) when it is refractory to conventional management (oral antihistamines and topical steroids). Aprepitant can alleviate symptoms significantly and improve associated comorbidities, such as insomnia, depression, and reduced quality of life, with few non-serious adverse effects or none. However, it is not considered a first-line therapy because of its high cost. Clinical studies used doses of 80 mg/day for 10-15 days, followed by 80 mg/48 h for 15-23 weeks or 125/80/80 mg every 2 weeks for 3 days for up to 6-24 weeks.

The use of scales²⁵⁻³⁷ is advised for the initiation and monitoring of assessments, along with a multidisciplinary approach (Table 2).

Regarding health-related quality of life, 38 patients with cutaneous lymphomas report multiple factors affecting their quality of life. The most common aspects include frustration (44%), concern on disease progression (43%), itching or pruritus (32%), and shame (28%).

One of the multimodal strategies used is integrative medicine, defined by the United States National Center for Complementary and Alternative Medicine as a combination of conventional and complementary approaches to treat the person as a whole rather than just an organ system³⁸. For cancer patients, this involves the use of vitamins, minerals, dietary changes, biological products (ie, teas, natural health products), and mind-body practices like qigong, mindfulness, and tai chi. Although specific integrative therapies in dermatologic oncology have not been studied extensively, there is medical literature available on their potential benefits in general

dermatology, such as promoting sleep in cancer patients. Additionally, the use of oral and topical therapies with evidence of scar-healing, anti-inflammatory, and anti-purpuric effects has also been described. Mind-body practices, including meditation and hypnosis, are believed to reduce discomfort and address psychosomatic aspects of skin disorders³⁹.

In palliative care, comprehensive models include symptomatic treatment alongside a general well-being perspective. Psychotherapy, especially counseling, is a widely used strategy to address emotional needs. Recently, however, “dignity therapy” has gained international recognition without statistically significant differences being reported in improving emotional well-being and distress. In this regard, the Patient Dignity Inventory is a tool used to measure suffering related to dignity in palliative care^{35,39,40}.

A cross-sectional study found that patients with MF who responded to the Skindex-29 survey (useful for skin symptoms, not specific to cutaneous lymphomas) and without evidence of the disease at the time of assessment scored higher in questions related to anger and fatigue²⁸.

In newly diagnosed patients, the following characteristics were associated with a worse quality of life: being female, elevated lactate dehydrogenase levels, alopecia, high scores in mSWAT (Modified Severity-Weighted Assessment Tool, useful for monitoring active CTCL), and confluent erythema. Female sex and alopecia were independent predictors of a worse overall quality of life. The cross-sectional studies of mixed populations showed that more advanced disease stage and pruritus were associated with worse health-related quality of life in patients with MF/SS^{29,30}.

In women, symptoms associated with worse health-related quality of life were burning/stinging, itching, irritation, and emotional effects such as feelings of depression, shame, and distress upon the diagnosis of MF/SS⁸. Although men can have a worse overall prognosis, we should mention that women with alopecia and more extensive cutaneous involvement had worse health-related quality of life regarding emotional, symptomatic, and functional impairment^{29,30}.

Multiple factors can impact the perception of quality of life in this population. However, due to the wide range of symptoms and individual factors affecting their sexual, social, spiritual, and emotional life across different stages of the disease, it is challenging to collect all these factors in a single tool. As a matter of fact, the tools currently available are not specific to this population and do not include caregiver or family observations^{40,41}.

There is a wide array of general quality of life measurement tools available for this population that can be used in the routine clinical practice as shown in table 2¹⁶. The FACT-Lym scale to assess quality of life in Colombian patients with lymphoma, although not specific to a particular population, has proven to be valid, reproducible, and sensitive in patients with MF/SS. Specific tools for this population include the Cutaneous Lymphoma Distress Questionnaire (CL-DQ) and the Mycosis Fungoides/Sézary Syndrome-Cutaneous T-Cell Lymphoma Quality of Life (MF/SS-CTCL QoL), with the limitation that they have not been validated in Spanish language yet³⁶.

The treating team should also address symptoms of sexual dysfunction associated with the disease. The PROMIS Sexual Function and Satisfaction (SexFS) scale evaluates sexual function and satisfaction in cancer patients, in both men and women. Depending on the complexity of sexual dysfunction, referrals to sexology or urology may be relevant depending on the anamnesis or results of this tool^{37,38}. Improving communication, awareness, and educational resources between the medical team and the patients are proven strategies that promote sexual health and help women and men cope with the side effects associated with treatment³⁹⁻⁴².

Discussion

As discussed above, MF and SS have few curative options, and treatments are primarily palliative. Therefore, treatment should focus on minimizing symptoms and improving quality of life. However, the current clinical guidelines for the management of CTCL do not include specific recommendations regarding the patients and their families or caregivers' supportive care needs⁴³.

Multidisciplinary assessment and management, addressing both physical and psychological functioning, are key to improve the care provided to patients and their caregivers. Early referrals to oncological dermatology, hematology, social work, psychology, or sexology can have a significant impact on the multidimensional aspects of quality of life beyond what standardized questionnaires show.

It is concerning that in this population, from an early stage like MF to SS, social stigmas can arise due to visible skin lesions, associated with the psychological or emotional issues of living with a chronic and potentially life-threatening disease, and often with financial difficulties and worsening symptoms associated with therapy⁴⁴⁻⁴⁶.

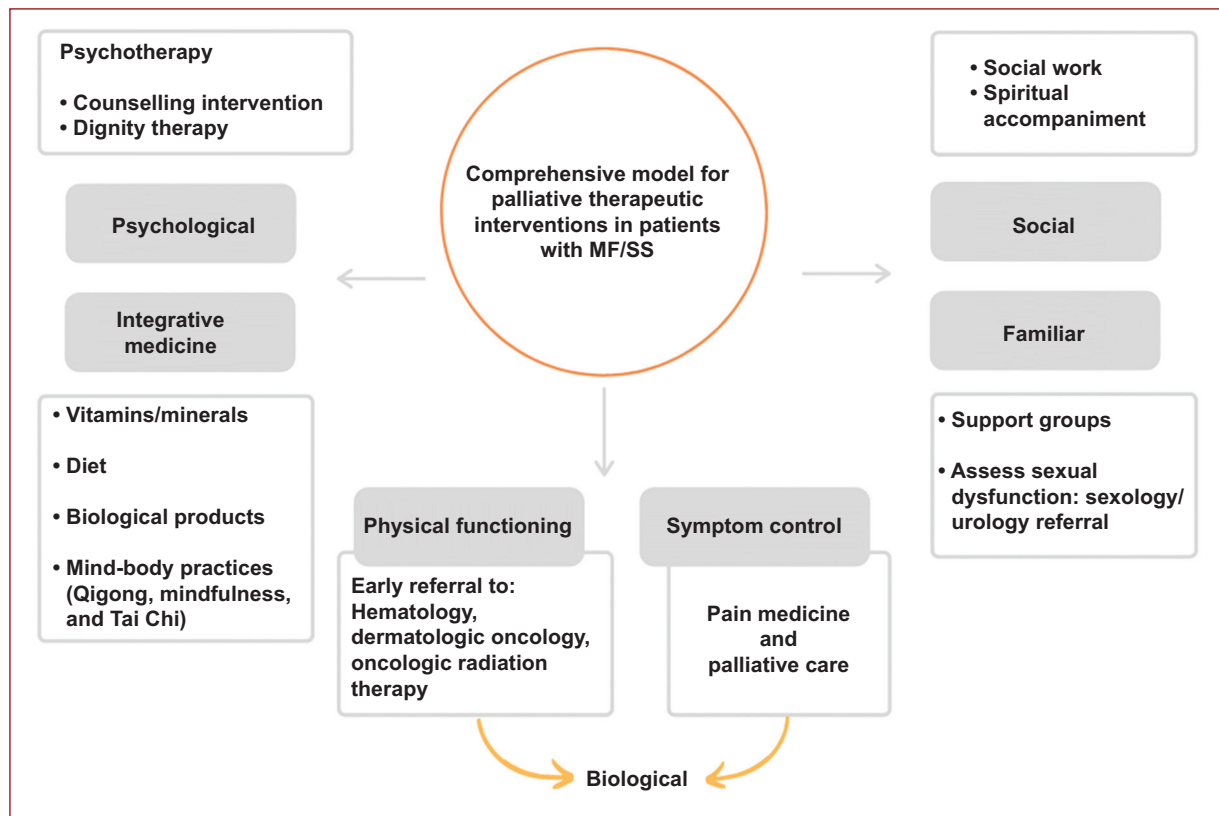


Figure 1. Comprehensive model proposal for palliative therapeutic interventions in patients with mycosis fungoides (MF) and Sézary syndrome (SS).

Therefore, it is crucial to objectively evaluate interventions that can improve the quality of life of this population using various scales such as the Skindex-29 or the Skindex-16 to assess skin involvement, presence of pruritus, and severity quantification through a visual analog scale, depending on the targeted treatment^{47,48}.

Early multidisciplinary treatment is recommended to monitor pharmacological and non-pharmacological strategies for symptom control and patient comfort. Psychological, social, and family aspects of care should be addressed too. Early referrals to pain medicine and palliative care units can improve the patients' overall quality of life significantly as shown in figure 1. This leads to the development of a comprehensive model for palliative therapeutic interventions, recognizing that CTCL impacts the patients' quality of life substantially, thus worsening as the disease progresses.

One limitation of this review is the scarcity of clinical trials to conduct a panoramic review or meta-analysis. The use of tools like FACT-Lym in a cohort of MF/SS patients treated with multidisciplinary palliative interventions is proposed to address this limitation.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this

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