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An Updated Review about the Management and Therapies of Mycosis Fungoides: Systematic Review

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Abstract: **Mycosis fungoides is the most typical cutaneous T-cell lymphoma. It is defined by sluggish progress over years to years, establishing from patches to infiltrated plaques, and sometimes to tumors. When lesions of refractory or relapsing mycosis fungoides are resistant to standard therapies, therapies such as localized chemotherapy, photochemotherapy and radiotherapy are typically used. These methods have acute or chronic side effects and toxicity, which might accumulate with duplicated and protracted treatment cycles. Photodynamic therapy is a promising, well endured choice for the treatment of localized sores with outstanding cosmetic results. In this article, we systematically examined and went over clinical application of photodynamic treatment in fallen back or refractory mycosis fungoides. There are 20 papers included in this review article.**

Keywords: **Mycosis fungoides, typical cutaneous T-cell lymphoma (CTCL).**

1. INTRODUCTION

Mycosis fungoides (MF) is a relatively uncommon, extranodal, non-Hodgkin's lymphoma with main cutaneous participation, which is usually indolent in behavior. It is a low-grade cutaneous T-cell lymphoma (CTCL) defined by small to medium sized cells with cerebriform nuclei that normally express mature peripheral CD4+ T-helper cell immunophenotypes and penetrate the skin characteristically with epidermotropism.[(1)] The incidence rate of MF has actually been reported to be 4.1/ 1, 000, 000 by a SEER (Surveillance, Epidemiology and End Results) based research study which used information from 16 pc registries in the United States to evaluate 3884 cases of CTCL from 2001-2005[(2)]. This makes MF the most typical cutaneous T-cell lymphoma (CTCL) subtype (54%). The threat of MF is connected with age, gender and race, with reasonably greater prevalence amongst the senior, males and blacks[(3)]. Occupational direct exposure, hereditary personality, radiation, and viral infection have been hypothesized as etiologic factors in relation to MF, while corresponding pathological system is yet to be elucidated[(4)].

The suitable treatment of MF is primarily based on prognostic factors, Tumor-Node visceral Metastases-Blood (TNMB) category, and total clinical stage at diagnosis[(5)]. The significant prognostic aspects reported by a big friend of 1,502 patents included increased age, male sex, increased lactate dehydrogenase (LDH), large-cell transformation and folliculotropic MF. These elements all reduce survival and increase the threat of disease development (RDP). Favorable prognostic elements consist of hypopigmented MF, MF with lymphomatoid papulosis, and poikilodermatous MF. These show improved survival and reduced RDP[(6)]. The latest version of staging and category was updated on 2008 by the World Health Organization (4th edn) and modified in 2010 [(7, 8)].

MF makes up the lengthy clinical evolution of spots, plaques, and tumors with a broad spectrum of potential clinical symptoms. MF patients are typically treated with a multimodal technique. Nevertheless, numerous patients go on to

establish resistance against a minimum of one type of treatment or have falling back symptoms after a duration of improvement. The treatment of fallen back or refractory MF has actually been really challenging due to the limited novel treatments readily available. In the past decade, clinical success has been reported utilizing photodynamic treatment (PDT) as a possible alternative non-invasive, target-specific therapy to treat MF. PDT utilizes reactive oxygen species generated by light-activated photosensitizer to oxidize essential cellular parts and consequently causes apoptosis and necrosis limited to target websites.

In 1994, Svanberg et al reported very first effective case of using topical δ-amino levulinic acid (ALA)based PDT to deal with an MF plaque [(9)]. In 1994, Boehncke et al discovered that the ability of PDT to hinder proliferation of T cells resembled that of PUVA both in vitro and in vivo[(10)] . In 1995, Rittenhouse-Diakun et al showed that malignant CTCL cells with increased CD71 expression, a marker of relative intracellular iron shortage, preferentially collected endogenously generated protoporphyrin IX (PpIX) and were extremely susceptible to ALA-PDT[(11)].In 2001, Gad et al showed a boost in caspase-3-like activities and boost in the percentage of DNA fragmentation in malignant T cells following ALA-PDT, which suggested that ALA-PDT might cause apoptosis and caspase activation[(12)]. Orenstein et al. observed various patterns of PpIX fluorescence in patients with innovative and early phases of the disease using 5-aminolevulinic acid topical application: in stage I MF lesions, no PpIX fluorescence was identified one hour after photoirradiation (580-720 nm), while in thick stage III lesions, PpIX fluorescence disappeared after an extra 10-15 minutes irradiation[(13)] . All these studies recommend the capability of PDT to selectively damage the deadly lymphocytes in MF lesions.

2. METHODOLOGY

We performed a systematic review of literature on May 25, 2016 and updated the search on September 10, 2016. We searched keywords “mycosis fungoides” and “photodynamic therapy” in PubMed (National Library of Medicine), Google-Scholar, Scopus, and Web of Knowledge databases. An article was considered to be eligible for inclusion if it met the following criteria: (A) therapy-resistant mycosis fungoides; (B) clinical PDT application; (C) English language. Review articles were excluded. A total of 20 papers were included in this review.

3. RESULTS AND DISCUSSION

ALA-photodynamic therapy:

In 1990, Kennedy and associates discovered and reported the porphyrin precursor ALA. This finding was an important milestone in the development of PDT in dermatology, as the small molecules might easily permeate the epidermis due to fairly low molecular weight[(14)] . ALA can be metabolized into photoactivatable porphyrins by the majority of cells as part of the heme cycle, and the levels of intracellular accumulation are relatively greater inside modified cells making up the infected tissue[(15)].

The very first case using ALA-PDT for effectively dealing with MF sores was reported in 1994, and since then many reports of effective ALA-PDT for patch/plaque stage MF have been published with great outcomes. Nevertheless, a variety of constraints impede the further application of ALA in PDT. For example, due to the fact that of poor tissue penetration, ALA cannot reach tumor tissue thicker than 3mm in order to cause enough necrosis. ALA requires an incubation period between application and light exposure to be metabolically transformed into the active PpIX, which causes the patients to wait for a long time[(16)].

MAL-photodynamic therapy:

A derivative of ALA, methyl ester methyl aminolevulinate (MAL), is reported to have increased lipophilicity and deeper skin penetration when compared to ALA. This enables a shorter incubation time and results in a much better selectivity toward growth cells[(17)]. In 2013, Ariel et al reported the very first case of tumor-stage MF sores that reacted successfully to topical MAL-PDT treatment[(18)]. MAL-PDT is therefore thought about as an alternative choice in picked cases of MF as well as in tumor-stage MF.

Light sources:

There is a large spectrum of light sources for PDT, including continuous-wavelength light sources (red, blue, white, or green), lasers, incoherent light sources and so on. To obtain preferred restorative impacts, the photosensitizing porphyrins

should be activated by light of a suitable wavelength. The porphyrins or related photosensitizers show an extremely typical absorption spectrum with the greatest peak at roughly 405 nm in the blue wavelength area, the so-called Soret-band, and numerous Q-bands with an absorption peak at 635 nm at a loss wavelength region[19]. It has been reported that compared to the blue spectrum, the traffic signal shows much better tissue penetration[20].

Additionally, laser and incoherent source of lights can be utilized in PDT. The benefit of laser is much shorter direct exposure time compared to incoherent source of lights, though the laser can not preferably match the porphyrin absorption spectrum. The development of intense pulsed light (IPL) devices (e.g. PDT 1200 l, Waldmann Medizintechnik) allows application of incoherent source of lights for PDT, with an emission spectrum ranging from 500 to 1300 nm. At present, the preferred light in topical PDT is incoherent light sources with wide illumination fields since this can accomplish the simultaneous irradiation of larger areas. Several studies have reported effective treatments of mycosis fungoides with IPL gadget for PDT[21, 22].In addition, the LED system of incoherent light sources (e.g. AktiliteTM, Galderma, Alby sur-Che´ran, France; Omnilux PDTTM, Phototherapeutics, Altrincham, UK) is a promising choice due to the fact that it releases only a narrow band of wavelengths that perfectly matches the absorption spectrum of porphyrins.

In addition, there is another type of photosensitizer for mycosis fungoides treatment under investigation. The silicon phthalocyanine Pc4, a second-generation photosensitizer, allows deeper tissue penetration of red light (λ= 675 nm; $\varepsilon = 2 \times 105$) when compared to PpIX or photofrin whose peak absorption in the red region is at 630 635nm[23].Pc4 accumulates in mitochondria to harm the anti-apoptotic proteins Bcl-2 and Bcl-xL, releases cytochrome c into the cytosol, and induces cellular apoptosis[24] .A stage 1 clinical trial of Pc4-PDT for mycosis fungoides was carried out in 2010 and showed the potential usefulness of topically delivered Pc4 to treat MF with good tolerability and promising effectiveness[25].

We discovered and reviewed 20 released short articles to reveal that PDT was useful as a skin restricted treatment in localized forms of MF that responded badly to regular treatments. Reported cases of successful treatment of relapsed or refractory MF plaques using PDT is summed up in *Table 1*. These research studies consisted of an overall of 81 patients previously treated with topical steroids, photochemotherapy, nitrogen mustard and so on. These patients had 117 fell back or refractory MF lesions which were treated with PDT, 78.6% (92/117) which were plaque-stage MF, 15.4%(18/117) of which were patch-stage MF, and the staying 6%(7/117) which were tumor-stage MF.

Given that the first case was reported in 1994 [26] and through 2006, 20% 5-ALA was used as the photosensitizer for PDT with 4-16 hours occlusion time. There were 9 research studies utilizing ALA, and 11 research studies utilizing MAL. 5-ALA has actually been replaced by MAL[30] with 3 hours occlusion time. This has actually increased lipophilicity and resulted in deeper skin penetration. Most of these research studies utilized long wavelengths around 600 nm by various light sources (red light, laser, and incoherent light), which could penetrate deeper and be more effective for the treatment of thicker lesions. The frequency of the treatment sessions was around every 2 to 4 weeks, and almost all the studies explained the requirement

for numerous sessions. Variety of sessions was connected with total light doses, type of sores, and level of sensitivity to the treatment. Repetitive sessions of PDT appeared to be mandatory in dealing with MF.

The overall complete response (CR) rate of the 117 MF lesions was 63.2% (60.9% in plaques, 72.2% in spots, and 71.4% in tumors, respectively). In theory, the correlation between CR rate and infiltrate depths of lesions should be negative. However, the publication predisposition might represent these observations. Edström et al observed a lower rate of action in growth phase sores, though all the tumor lesions revealed regression[31] . Follow-up duration of each research study varies from 3 months post-treatment to 87 months. Therefore, PDT can be an important treatment choice for fallen back or refractory MF at various clinical phases, especially for patch or plaque-stage, although optimal specifications of PDT have actually not yet been defined.

Table 1 Studies demonstrating the effect of PDT in the treatment of relapsed or refractory MF

Study	Number of lesions/ Number of patients	Previous treatments	Light / Light doses	Photosen sitizer/ Application duration	Number of PDT sessions	Type of lesions	Percentage of CR	Follow-up period (months)
Wolf et al., 1994[26]	3/2	Topical steroids, UVB phototherapy, and PUVA	Visible light/4 0 J/cm2	20% ALA cream/ 4-6 hours	4-5	3 plaques	CR 3/3 (100%)	3-6

Han et al., 2016[43]	3/3	PUVA, and interferon	Red light, 635nm /60nw /cm2	20% ALA solution/ 4 hours	2-3	3 plaques	CR 2/3 (66.7%)	8-17
Jang et al., 2015[42]	1/1	Topical steroid	Red light, 570- 670 nm / 37 J/cm2	MAL cream/ 4 hours	2	1 patch	CR 1/1 (100%)	/
Jung et al., 2015[41]	1/1	Eight treatment sessions with a 308- nm excimer laser	Red light, 630 nm/37 J/cm2	20% MAL cream/ 1.5 hours	8	1 tumor	CR 1/1 (100%)	/
uéreu x et al., 2013([40]	12/7	Bexarotene, and interferon	Red light, 630 nm/37 J/cm2	20% MAL cream/ 3 hours	2-6	5 plaques, 7 patches	5/5 plaques CR (100%), 4/7 patches CR (57.1%)	10-35
Ariel et al., 2013[39]	1/1	Psoralen + ultraviolet A, bexarotene, and total- skin electron beam radiation	Incoherent light, 570-670 nm /37J /cm2	160 mg/g MAL cream/ 3 hours	3	1 tumor	CR 1/1 (100%)	60
Calzava ra-Pinton et al., 2013[38]	19/19	Resistant to previous treatments	Red light, 635± 18 nm/ 37 J/cm2	20% MAL cream/ 3-4 hours	1-7	19 plaques	CR 5/19 (26%)	20 (2 CR patient s relapse d)

Discussion:

For mycosis fungoides, multiple treatment modalities such as PUVA, interferon, systemic chemotherapy, and total body electron beam irradiation may fail to control all lesions in some patients, so additional localized therapies may be required. PDT is a recently introduced therapeutic modality that has been proven effective and well tolerated in patients with localized relapsed or refractory MF lesions, even in tumor-stage. The advantages of PDT include excellent cosmetic results, noninvasive nature, excellent selectivity, low risk of toxicity accumulation, and negligible generalized photosensitivity, and low carcinogenic potential. These advantages make PDT a valuable therapeutic option in difficult-to-treat subsets of MF, such as relapsed or refractory MF, or even in sensitive areas such as the face and neck[34].

4. CONCLUSION

In conclusion, PDT is a promising treatment option for relapsed or refractory mycosis fungoides. Despite the relative simplicity of the technique, established treatment protocols have not yet been optimized for PDT in MF with respect to ALA or MAL application time, light dosimetry, delivery, frequency of treatment, and number of sessions. Therefore, larger clinical studies are required and the optimal treatment regimens need to be clarified.

REFERENCES

[1] Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. N Engl J Med 2004; 350: 1978–1988.

[2] Barton PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population based study of 3884 cases. Blood 2009; 113: 5064–5073.

[3] Weinstock MA, Horm JW: Mycosis fungoides in the United States. JAMA 1988; 60: 42–46.

[4] Morales Suarez-Varela MM, Llopis Gonzalez A, Marquina Vila A, Bell J. Mycosis fungoides: review of epidemiological observations. Dermatology 2000; 201: 21-28.

[5] Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sézary syndrome: a stage-based approach. J Natl Compr Canc Netw 2008 Apr; 6: 436-442.

[6] Agar NS, Wedgeworth E, Crichton S et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010; 28: 4730–4739.

[7] Swerdlow SH, Campo E, Harris NL et al. WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. Lyon: IARC Press, 2008.

[8] Kempf W, Sander CA. Classification of cutaneous lymphomas - an update. Histopathology 2010; 56: 57-70.

[9] Svanberg K, Andersson T, Killander D et al. Photodynamic therapy of non-melanoma malignant tumours of the skin using topical delta-amino levulinic acid sensitization and laser irradiation. Br J Dermatol 1994; 130: 743–751.

[10] Boehncke WH, Konig K, Ruck A, Kauffman R, Sterry W. In vitro and in vivo effects of photodynamic therapy in cutaneous T cell lymphoma. Acta Derm Venereol 1994; 74: 201–205.

[11] Rittenhouse-Diakun K, Van Leengoed H, Morgan J et al. The role of transferrin receptor (CD71) in photodynamic therapy of activated and malignant lymphocytes using the heme precursor delta-amino-levulinic acid (ALA). Photochem Photobiol 1995; 61: 523–528.

[12] Gad F, Viau G, Boushira M, Bertrand R, Bissonnette R. Photodynamic therapy with 5- aminolevulinic acid induces apoptosis and caspase activation in malignant T cells. J Cutan Med Surg 2001; 5: 8-13.

[13] Orenstein A, Haik J, Tamir J, et al. Photodynamic therapy of cutaneous lymphoma using 5-aminolevulinic acid topical application. Dermatol Surg 2000; 26: 765-769.

[14] Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B 1990; 6: 143–148.

[15] Babilas P, Karrer S, Sidoroff A, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology--an update. Photodermatol Photoimmunol Photomed 2005; 21: 142- 149.

[16] Babilas P, Schreml S, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology: state-of-the-art. Photodermatol Photoimmunol Photomed 2010; 26: 118–132.

[17] Peng Q, Soler AM, Warloe T, Nesland JM, Giercksky KE. Selective distribution of porphyrins in skin thick basal cell carcinoma after topical application of methyl 5- aminolevulinate. J Photochem Photobiol B 2001; 62: 140-145.

[18] Ariel Hasson, Cristián Navarrete-Dechent, Claudia Nicklas et al. Topical photodynamic therapy with 5-aminolevulinate for the treatment of tumor-stage mycosis fungoides: a case report. Int J Dermatol 2013; 52: 1535-1537.

[19] Szeimies RM, Abels C, Fritsch C et al. Wavelength dependency of photodynamic effects after sensitization with 5-aminolevulinic acid in vitro and in vivo. J Invest Dermatol 1995; 105: 672–677.

[20] Brown SB. The role of light in the treatment of non-melanoma skin cancer using methyl aminolevulinate. J Dermatolog Treat 2003; 14 Suppl 3: 11–14.

[21] Markham T, Sheahan K, Collins P. Topical 5-aminolaevulinic acid photodynamic therapy for tumor-stage mycosis fungoides. Br J Dermatol 2001; 144: 1262–1263.

[22] Coors EA, von den Driesch P. Topical photodynamic therapy for patients with therapy-resistant lesions of cutaneous T-cell lymphoma. J Am Acad Dermatol 2004; 50: 363–367.

[23] N. L. Oleinick, A. R. Antunez, M. E. Clay, B. D. Rihter, M. E. Kenney. New phthalocyanine photosensitizers for photodynamic therapy. Photochem Photobiol 1993; 57: 242- 247.

[24] Oleinick NL, Morris RL, Belichenko I. The role of apoptosis in response to photodynamic therapy: What, where, why and how. Photochem Photobiol Sci 2002; 1:1–21.

[25] Baron ED, Malbasa CL, Santo-Domingo D, et al. Silicon Phthalocyanine (Pc 4) Photodynamic Therapy Is a Safe Modality for Cutaneous Neoplasms: Results of a Phase 1 Clinical Trial. Lasers Surg Med 2010; 42: 728–735.

[26] Wolf P, Fink-Puches R, Cerroni L, Kerl H. Photodynamic therapy for mycosis fungoides after photosensitization with 5-aminolevulinic acid. J Am Acad Dermatol 1994; 31: 678–680.

[27] Wang I, Bauer B, Anderson-Engels S, Svanberg S, Svanberg K. Photodynamic therapy utilizing delta aminolevulinic acid in non-melanoma skins malignancies of the eyelid and periocular skin. Acta Ophthalmol Scand 1999; 77: 182–188.

[28] Orenstein A, Haik J, Tamir J et al. Photodynamic therapy of cutaneous lymphoma using 5-aminolevulinic acid topical application. Dermatol Surg 2000; 26: 765–769.

[29] Leman JA, Dick DC, Morton CA. Topical 5-ALA therapy for the treatment of cutaneous T-cell lymphoma. Clin Exp Dermatol 2002; 27: 516–518.

[30] Zane C, Venturini M, Sala R, Calzavara-Pinton P. Photodynamic therapy with mehtylaminolevulinate as a value treatment option for unilesional cutaneous T-cell lymphoma. Photodermatol Photoinmunol Photomed 2006; 22: 254–258.

[31] Edström DW, Hedblad MA. Long-term follow-up of photodynamic therapy for mycosis fungoides. Acta Derm Venereol 2008; 88: 288-290.

[32] Recio ED, Zambrano B, Alonso ML et al. Topical 5-aminolevulinic acid photodynamic therapy for the treatment of unilesional mycosis fungoides: a report of two cases and review of the literature. Int J Dermatol 2008; 47: 410–413.

[33] Hegyi J, Frey T, Arenberger P. Unilesional mycosis fungoides treated with photodynamic therapy. A case report. Acta Dermatovenerol Alp Panonica Adriat 2008; 17: 75–78.

[34] Debu A, Girard C, Kluger N, Guillot B, Dereure O. Topical methyl aminolaevulinate- photodynamic therapy in erosive facial mycosis fungoides. Br J Dermatol 2010; 163: 884–885.

[35] Fernández-Guarino M, Harto A, Pérez-García B, Montull C, De Las Heras E, Jaén P. Plaque-Phase Mycosis Fungoides Treated with Photodynamic Therapy: Results from 12 Patients. Actas Dermosifiliogr 2010; 101: 785-91.

[36] Kim ST, Kang DY, Kang JS, Baek JW, Jeon YS, Suh KS. Photodynamic therapy with methyl-aminolaevulinic acid for mycosis fungoides. Acta Derm Venereol 2012; 92: 264-268.

[37] Debu A, Bessis D, Girard C, Du Thanh A, Guillot B, Dereure O. Photodynamic therapy with methyl aminolaevulinate for cervical and/or facial lesions of folliculotropic mycosis fungoides: interest and limits. Br J Dermatol 2013; 168: 896-8.

[38] Calzavara-Pinton PG, Rossi MT, Sala R; Italian Group For Photodynamic Therapy. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 2: oncologic and infectious indications. Photochem Photobiol Sci 2013; 12: 158-65.

[39] Ariel Hasson, Cristián Navarrete-Dechent, Claudia Nicklas et al. Topical photodynamic therapy with 5-aminolevulinate for the treatment of tumor-stage mycosis fungoides: a case report. Int J Dermatol 2013; 52: 1535-1537.

[40] Quéreux G, Brocard A, Saint-Jean M, et al. Photodynamic therapy with methyl- aminolevulinic acid for paucilesional mycosis fungoides: a prospective open study and review of the literature. J Am Acad Dermatol 2013; 69: 890–897.

[41] Jung SE, Kim YC. A case of pagetoid reticulosis treated with fractional laser-assisted photodynamic therapy. Clin Exp Dermatol 2015; 40: 468-70.

[42] Jang S, Hwang EJ, Ryu HH, Cho KH, Jo SJ. A Case of Unilesional Mycosis Fungoides Treated with Photodynamic Therapy Using Methyl-Aminolevulinate. Korean J Dermatol 2015; 53: 58-61.

[43] Han D, Xue J, Wang T, Liu Y. Observation of clinical efficacy of photodynamic therapy in 3 patients with refractory plaque-stage mycosis fungoides. Photodiagnosis Photodyn Ther 2016; 16: 9-11.