PHOTODYNAMIC THERAPY IN THE TREATMENT OF PATIENTS WITH MYCOSIS FUNGOIDES

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Abstract

The review highlights the current understanding of the epidemiology, etiology, pathogenesis, existing classifications of mycosis fungoides. Methods for diagnosis and treatment of the pathology are described, among which photodynamic therapy (PDT) plays an important role. The main advantages of PDT for mycosis fungoides include the absence of systemic toxicity, non-invasiveness, selectivity, absence of carcinogenic potential, the possibility of repeated courses of treatment, and good cosmetic results. This review collects and analyzes the results of clinical trials of PDT in patients with mycosis fungoides. The analysis showed high efficiency of PDT in patients with mycosis fungoides with isolated or limited spots and plaques. PDT can be considered as the therapy of choice in patients with facial lesions when a good cosmetic result is one of the main requirements, and radiation therapy, nitrogen mustard or carmustine can leave permanent and visible scars. Plaques located in the axillary or inguinal skin folds that are inaccessible to phototherapy can also be treated with PDT.

Key words: photodynamic therapy, mycosis fungoides, 5-aminolevulinic acid.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ В ЛЕЧЕНИИ БОЛЬНЫХ ГРИБОВИДНЫМ МИКОЗОМ

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Резюме

В обзоре освещены современные представления об эпидемиологии, этиологии, патогенезе, существующих классификациях грибовидного микоза. Описаны методы диагностики и лечения патологии, важную роль среди которых играет фотодинамическая терапия (ФДТ). К основным преимуществам ФДТ грибовидного микоза относятся отсутствие системной токсичности, неинвазивность, избирательность действия, отсутствие канцерогенного потенциала, возможность проведения повторных курсов лечения и хорошие косметические результаты. В настоящем обзоре собраны и проанализированы результаты клинических исследований ФДТ пациентов с грибовидным микозом. Анализ показал высокую эффективность ФДТ у пациентов с грибовидным микозом с изолированными или ограниченными пятнами и бляшками. ФДТ можно рассматривать как терапию выбора у пациентов с очагами на лице, когда одним из основных требований является хороший косметический результат, а лучевая терапия, азотный иприт или кармустин могут оставить постоянные и видимые шрамы. Бляшки, расположенные в подмышечных или паховых складках кожи, недоступные для фототерапии, также можно лечить с помощью ФДТ.

Ключевые слова: фотодинамическая терапия, грибовидный микоз, 5-аминолевулиновая кислота.

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Mycosis fungoides (MF) is a primary epidermotropic T-cell lymphoma of the skin, characterized by the proliferation of small and medium T-lymphocytes with cerebriform nuclei. MF is one of the most common forms of cutaneous T-cell lymphomas. In the earliest stages of the disease, patients usually present with isolated skin lesions resembling eczema or extensive erythema [1]. The term "mycosis fungoides" was introduced by J.L.M. Alibert in 1832 in relation to the unusual skin rash he described in 1806, which developed into tumors in the form of mushrooms [2].

Epidemiology

After the gastrointestinal tract, the skin is the second most common site of extranodal non-Hodgkin's lymphoma, with an estimated annual incidence of 1 case per 100,000 population. According to the fourth edition of the WHO Blue Book, MF is the most common form of primary cutaneous lymphomas (skin lymphomas without evidence of extracutaneous disease at the time of diagnosis) according to the classification of skin tumors. The proportion of MF in the overall incidence of primary cutaneous lymphomas is 53% of primary cutaneous T-cell lymphomas and 45% of all primary cutaneous lymphomas (of which 39% is the classic form of MF, 6% are its variants according to the WHO-EORTC classification, including folliculotropic MF – 5%, pagetoid reticulosis – less than 1%, granulomatous loose skin syndrome – less than 1%) (Table 1). Another 20% of primary cutaneous cutaneous lymphomas are due to primary cutaneous $CD30^+$-lymphoproliferative diseases, including 8% to primary cutaneous anaplastic large cell lymphoma° 12% to lymphomatoid papulosis; 6% for primary cutaneous $CD4^+$ T-cell lymphoproliferative disease of small and medium cells; 2% for Cesari's syndrome; 9% – for primary B-cell lymphoma of the marginal zone of the skin; 12% – for primary cutaneous lymphoma from the cells of the follicular center; 4% – for primary cutaneous diffuse large B-cell lymphoma, lower extremity type. The incidence of other types of primary cellular lymphomas is less than 1% for each type [3, 4].

Classification

In 1876, Bazin described three classical stages in the development of MF: macules, infiltrated plaques, and tumors. Each of them differs from the previous one by increasing thickness. Stages can overlap or register at the same time. If only tumors are present, with no preceding or coexisting macules or plaques, the diagnosis of MF should be questioned. WHO and the European Organization for Research and Treatment of Cancer, in addition to the classical form of Albert-Bazen MF, characterized by the development of spots, plaques and tumors, distinguish three variants of the disease: folliculotropic MF, pagetoid reticulosis, and granulomatous flaccid skin syndrome [1, 2, 5].

Clinical picture

MF usually presents clinically as persistent patches or plaques that are sometimes itchy and usually affect areas of the skin that are not exposed to sunlight. These lesions can often remain unchanged for many years or even throughout the life of the patient, but progression to disseminated lesions, tumor development, or lesions of internal organs can occur, which worsens the prognosis and requires systemic treatment [6]

Diagnosis

Diagnosis of MF is usually based on characteristic clinical manifestations and confirmed by routine histology [2]. The gold standard is light microscopy of affected skin sections stained with hematoxylin-eosin, but early diagnosis can be difficult because the initial histological picture may resemble other chronic inflammatory dermatoses [1, 2]. To date, there are no diagnostically significant molecular markers that can reliably distinguish between malignant and benign T cells [1]. The histological picture is more often diagnostically significant at the plaque stage. In this case, histology reveals a streak-like or lichenoid infiltrate of mononuclear cells in the papillary dermis with overlying epidermotropism (intraepidermal lymphocytes with slight spongiosis). These lymphocytes are found individually or in clusters within the epidermis, often surrounded by a clear halo (Pauttier microabscesses). When examining mononuclear cells at high magnification, hyperchromatic and irregular contours of the nuclei are revealed. The picture of psoriasiform hyperplasia of the epidermis with hyperkeratosis and focal parakeratosis is determined [2].

Traditional treatment

Most cases of MF are characterized by a sluggish course with a low risk of disease progression, but complete regression is rarely achieved. Therefore, the main goal of treatment is to minimize symptomatic morbidity and limit disease progression [1].

The variability of the clinical picture and the clinical course of MF has led to the emergence of many schemes and complex treatment algorithms. It is important to understand that very little clinical research has been done on MF to date, as it is a fairly rare condition and the evidence on which current treatment recommendations are based is limited [6].

Treatment methods used in MF can be divided into topical, skin-directed, and systemic therapies.

For the treatment of stage IA, IIA, IIB MF, 2 types of skin-directed therapy are traditionally used: for a localized form (IA) and for a widespread (IIA, IIB) lesion (Table 1).

The most common treatment for the early stages of MF (stages IA-IIA) are topical corticosteroids [6, 14]. Most often they are used as an adjunct to other

Таблица 1
Рекомендации по лечению грибовидного микоза IA, IIA, IIB стадии [6,10-13]
Table 1
Treatments for early mycosis fungoides (stages IA, IIA, IIB) [6,10-13]

Локализованная форма Localized disease	Распространенная форма Widespread disease
Местное применение кортикостероидов Topical corticosteroids	Местное применение кортикостероидов Topical corticosteroids
Местная химиотерапия (азотный иприт, кармустин) Topical chemotherapy (nitrogen mustard, carmustine)	Местная химиотерапия (азотный иприт, кармустин) Topical chemotherapy (nitrogen mustard, carmustine)
Локальная лучевая терапия Local radiotherapy	Фототерапия: UVB, псорален–UVA Phototherapy: UVB, psoralen–UVA
Местное применение ретиноидов (бексаротен, тазаротен) Topical retinoids (bexarotene, tazarotene)	Тотальная кожная электронно-лучевая терапия Total electron-beam skin therapy
Фототерапия: UVB, псорален–UVA Phototherapy: UVB, psoralen–UVA	
Местное применение имиквимода Topical imiquimod	

local and systemic treatments at all stages. They induce apoptosis, affect the adhesion of lymphocytes to the endothelium and suppress transcription factors (nuclear factor-kB and activator protein-1), reduce the production of cytokines, adhesion molecules and growth factor. Nitrogen mustard therapy and phototherapy are also often used, which, according to some authors, have the same efficacy in early MF and are used in combination with additional maintenance therapy necessary to achieve long-term complete remissions. Phototherapy (narrow-band UVB or psoralen-UVA) alone or in combination with systemic therapy (bexarotene, interferon, or methotrexate) is effective for widespread plaques [6]. PUVA therapy demonstrates low efficiency when used at the stage of the tumor or erythrodermic and folliculotropic MF; however, studies show its effectiveness in combination with low doses of systemic agents, such as interferon-alpha [14, 15]. Total skin electron beam therapy at a standard dose of 30 Gy is an effective treatment for obstinate/recurrent extensive plaques and fungal tumor mycoses, but is associated with significant dermal toxicity. This type of therapy reduces the number of circulating abnormal T cells that pass through the vasculature of the dermis and are radiosensitive. However, there are conflicting reports on its efficacy in erythrodermic MF. For isolated lesions, low-dose local radiation therapy may also be useful [14].

Systemic therapy of MF is carried out both separately and in the form of complex treatment. If skin-targeted therapy does not provide an adequate response or in cases of advanced disease, single-component systemic therapy (eg, bexarotene) is prescribed. Immunomodulators such as interferons and retinoids are also commonly used as first-line monotherapy for advanced forms of MF, as well as in low dose combinations with topical agents. Histone deacetylase inhibitors (vorinostat or romidepsin) are also effective agents for monotherapy in cutaneous and nodular forms of MF and forms of the disease with blood involvement. Alemtuzumab is an effective drug for erythrodermic mycosis fungoides with a deficit of central memory T cell population. Chemotherapy is usually used to treat obstinate or rapidly progressive MF. In advanced forms of MF, allogeneic stem cell transplantation can be effective [14].

Many of the traditional MF therapies described above show insufficient efficacy and are accompanied by long-term side effects. This is especially true of lesions located in places such as the palms and soles of the feet. This necessitates the search for alternative treatment options for mycosis fungoides.

Photodynamic therapy

PDT is an effective and non-invasive method of exposure with good clinical results [16].

The mechanism of photodynamic effects in MF is not fully understood. It is possible that, in addition to the direct destruction of pathological lymphocytes due to the generation of reactive oxygen species, the inflammatory response induced by PDT contributes to the therapeutic effect [17-20].

In 1994, Boenhcke et al. demonstrated how PDT inhibits lymphocyte proliferation in MF plaques both *in vivo* and *in vitro* [21].

M. Lam et al. studied the mechanisms of photocytotoxicity of the silicon-phthalocyanine photosensitizer Pc 4 in relation to pathological T-lymphocytes in the skin cell culture of patients with MF. Studies have shown that PDT with PC 4 predominantly induces apoptosis of $CD4^+$ $CD7^-$ transformed T-lymphocytes in the blood compared to $CD11b^+$ monocytes and normal T-cells, that is, selectively affects pathological T-lymphocytes. It was also shown that PDT with Pc4 reduced the level of the antiapoptotic protein Bcl-2 [22].

The high efficiency and absence of systemic toxicity of PDT are due to the selective accumulation of photosensitizers in the lesions and local exposure to light [17].

For PDT of MF, preparations based on 5-aminolevulinic acid (5-ALA) and 5-ALA methyl ester are usually used. 5-ALA methyl ester has more pronounced lipophilic properties, shorter incubation time and higher selectivity for pathological lymphocytes compared to 5-ALA. Both of these drugs are metabolized in the human body with the formation of photoactive protoporphyrin IX [17].

The selectivity of the accumulation of protoporphyrin IX in pathological lymphocytes in the foci of MF is due to a number of factors. Protoporphyrin IX is more actively synthesized in transformed lymphocytes. This is due to excessive iron intake due to increased expression of the CD71 transferrin receptor [23], increased activity of porphobilinogen deaminase, an enzyme that limits the rate of heme synthesis [24], and acceleration of the cell cycle in cells, which increases their ability to absorb 5-ALA [6, 25].

In addition, changes in the stratum corneum of the epidermis in plaques contribute to the penetration of the photosensitizer into the skin [6, 26].

Evaluation of the effectiveness of PDT is carried out on the basis of a clinical picture demonstrating the disappearance of MF foci, and a histological examination. A number of authors believe that the assessment of the clinical response is sufficient and reflects the real effectiveness of the treatment. According to other researchers, in evaluating the effectiveness of MF treatment, the histological therapeutic response is more important than the clinical response.

Histological response to treatment has been evaluated in a number of studies, but the small number of observations and conflicting data obtained by different investigators do not allow an unambiguous conclusion to be made about the need to confirm clinical response by histological examination.

R. Ammann et al. and E. Diez-Recio et al. reported a complete histological treatment and the absence of atypical lymphocyte infiltrates in all MF plaques after PDT with 5-ALA in 3 patients whose clinical outcome was assessed as complete regression. Both groups of researchers described pigmentary changes with the presence of melanophages, skin fibrosis, epidermal atrophy, and residual lymphocytes in the infiltrate [27, 28].

Concurrently S.T. Kim et al. believe that the final decision to assess the effect of treatment as a complete or partial regression should be determined by the results of histological analysis [17]. According to the results obtained, 7 out of 10 patients with unilateral MF showed an obvious improvement in their condition. Most previous studies did not follow up histologically. In the described study, 8 out of 10 patients underwent histological observation, and only 5 of them had a clinical and histological response that coincided and could be assessed as a complete regression. In 2 patients with full therapeutic clinical effect, the histological report showed partial regression of the lesions. D.W. Edstrom et al. also found a residual infiltrate of atypical lymphocytes in 2 patients after PDT with 5-ALA in lesions that showed a complete clinical response [29]. Possibly, these results are related to the insufficient depth of light penetration for selective action on lymphocytes in MF plaques. D. Eich et al. treated 8 patients with tumor form of MF. A subsequent biopsy showed the absence of histological signs of GM in the infiltrate up to a depth of 1.5 mm, while atypical lymphocytes continued to be detected in deeper tissues [30]. Published data do not clearly prove that with complete clinical regression of MF foci after PDT, atypical lymphocytes in the foci were completely eliminated, and therefore patients with a complete clinical response after PDT should be under dynamic monitoring for timely detection of a possible relapse [6].

Table 2 summarizes the results of the main clinical studies presented in the Pubmed database evaluating the effectiveness of PDT for MF. These studies include a total of data from 71 patients with 120 MF lesions treated with PDT from 1994 to 2018. Most of the authors used red light sources (coherent and incoherent). In earlier works, preparations based on 5-ALA were used. Since 2006, most studies have used 5-ALA methyl ester. The number of PDT courses varied from 1 to 9. A light dose of 37 J/cm^2 was predominantly used; in some cases, the light dose during irradiation was higher and reached 200 J/cm^2.

The conducted studies show the promise of using PDT as one of the options for localized skin-targeted therapy. In the late stages of advanced MF (stage IIB and above), PDT is of less interest due to the complexity of influencing the generalized process; however, it can be used as a treatment for individual plaques or tumors [6].

Due to the small number of observations and the

lack of large-scale clinical studies of the effectiveness of PDT in patients with MF, the optimal modes of PDT have not yet been determined [17]. It can be noted that the high efficiency of treatment was achieved using drugs based on both 5-ALA and 5-ALA methyl ester. The light dose and the frequency of courses varied significantly in different studies, and therefore it is difficult to determine whether there is a correlation between these indicators and the effectiveness of treatment, although most authors indicated the need for several courses of PDT.

Patients generally tolerate PDT well, although most studies report a slight burning sensation during the procedure. After PDT, some patients developed erythema and edema at the treatment site, much less often – scabs and erosion. Studies have shown that lesions can develop mild pigmentary changes, most often hyperpigmentation or hair loss [16, 17, 27-29, 31-43].

There have been several studies evaluating the effectiveness of fluorescence diagnosis of MF.

The fluorescence pattern of MF foci was described by A. Orestein et al. as weak and diffuse in spots, intense with well-defined boundaries in plaques and tumors [34]. The authors reported that when irradiated during a PDT session, the fluorescence intensity decreased faster in spots and plaques than in tumors.

In the studies of Svanberg K. et al. the fluorescent contrast of MF foci after exposure to 20% exposure with 5-ALA was 5.0 [31].

Таблица 2
Сводные данные результативности применения фотодинамической терапии у пациентов с грибовидным микозом
Table 2
Summary of the effectiveness of photodynamic therapy in patients with mycosis fungoides

Авторы Authors	Количество очагов/ пациентов No. of lesions/ No. of patients	Фотосенсибилизатор Photosensitizer	Режим облучения Irradiation mode	Световая доза, Дж/см² Light dose, J/cm²	Количество курсов ФДТ Number of PDT courses	Тип очага Type of lesion	Результат терапии, % пациентов Results of therapy, % of patients	Срок наблюдения, мес Follow-up period, month
Svanberg и соавт., 1994 [31]	4/2	5-АЛК 5-ALA	Лазер, 630 нм Laser, 630 nm	60	1-2	Не указан Not specified	ПР 50% (1/2) CR 50% (1/2)	Не указан Not specified
Wolf и соавт., 1994 [32]	2/2	5-АЛК 5-ALA	Видимый свет Visible light	40	4-5	Бляшка Plaque	ПР 100% CR 100%	3–6
Amman и соавт., 1995 [27]	1/1	5-АЛК 5-ALA	Видимый свет Visible light	Не указана Not specified	1	Бляшка Plaque	CR 100%	Не указан Not specified
Wang и соавт., 1999 [33]	3/1	5-АЛК 5-ALA	Лазер, 635 нм Laser, 635 nm	60	3-4	Бляшки Plaques	CR 100%	17-33
Markham и соавт., 2001 [35]	1/1	5-АЛК 5-ALA	Некогерентный источник света, 580-740 нм Noncoherent light, 580–740 nm	20	5	Опухоль Tumor	ПР 100% CR 100%	12 В течение 12 мес наблюдения возник рецидив (пятно и бляшка). During the 12 months of follow-up, a relapse occurred (patch and plaque).
Edstrom и соавт., 2001 [29]	12/10	5-АЛК 5-ALA	Некогерентный источник света, 600-730 нм Noncoherent light, 600–730 nm	33-180	2-11	10 бляшек 2 опухоли 10 plaques 2 tumors	**Бляшки:** ПР 70% (7/10) ЧР 20% (2/10) не оценен 10% (1/10) **Опухоли:** отсутствие эффекта 100% (2/2) **Plaques:** CR 70% (7/10) PR 20% (2/10) not rated 10% (1/10) **Tumors:** no effect 100% (2/2)	4–19

Авторы Authors	Количество очагов/ пациентов No. of lesions/ No. of patients	Фотосенсибилизатор Photosensitizer	Режим облучения Irradiation mode	Световая доза, Дж/см² Light dose, J/cm²	Количество курсов ФДТ Number of PDT courses	Тип очага Type of lesion	Результат терапии, % пациентов Results of therapy, % of patients	Срок наблюдения, мес Follow-up period, month
Leman и соавт., 2002 [36]	2/1	5-АЛК 5-ALA	Лазер, 630 нм Laser, 630 nm	100	4	Пятна Patches	ПР 100% CR 100%	12
Coors и соавт., 2004 [37]	7/4	5-АЛК 5-ALA	Некогерентный источник света, 60-160 нм Noncoherent light, 60–160 nm	72-144	1-7	Бляшки Опухоли Plaques Tumors	ПР 100% CR 100%	14–18
Zane и соавт., 2006 [38]	5/5	Метиловый эфир 5-АЛК 5-ALA methyl ester	Лазер, 635 нм Laser, 635 nm	37,5	1-9	Пятна Patches	ПР 80% (4/5) ЧР 20% (1/5) CR 80% (4/5) PR 20% (1/5)	12–34
Díez-Recio и соавт., 2007 [28]	2/2	5-АЛК 5-ALA	Импульсный лазер на красителе, 585 нм Pulsed dye laser, 585 nm	8 Дж/см², длительность импульса 0,45 мс, степень перекрытия импульсов 1 Гц, количество импульсов 8-22 8 J/cm², pulse duration of 0.45 ms, degree of pulse overlap of 1 Hz 8-22 pulses per treatment	3	Бляшки Plaques	ПР 100% CR 100%	34
Hegyi J. и соавт., 2008 [42]	1/1	Метиловый эфир 5-АЛК 5-ALA methyl ester	Светодиод, 630 нм LED, 630 nm	100-200	3	Пятно Patche	ПР 100% CR 100%	16
Orenstein и соавт., 2009 [34]	6/2	5-АЛК 5-ALA	Некогерентный источник света, 580-720 нм Noncoherent light, 580–720 nm	170 (пятно) 380 (опухоли) 170 (patch) 380 (tumors)	1 (пятно) Фракционное облучение (опухоли) 1 (patch) Fractional irradiation (tumors)	1 пятно 5 опухолей 1 patch 5 tumors	ПР 100% CR 100%	24-27
Fernández-Guarino и соавт., 2010 [39]	24/12	Метиловый эфир 5-АЛК 5-ALA methyl ester	Лазер, 630 нм Laser, 630 nm	37	В среднем 5,7 Mean 5,7	Бляшки Plaques	ПР 50% (6/12) ЧР 42% (5/12) CR 50% (6/12) PR 42% (5/12)	6–36
Kim и соавт., 2012 [17]	16/10	Метиловый эфир 5-АЛК 5-ALA methyl ester	Светодиод, 630 нм LED, 630 nm	37,5	2-6	6 пятен 10 бляшек 6 patches 10 plaques	**По очагам:** ПР 13% (2/16) ЧР 31% (5/16) отсутствие эффекта 56% (9/16) CR 13% (2/16) PR 31% (5/16) no effect 56% (9/16) **Или по пациентам:** ПР 20% (2/10) ЧЭ 50% (5/10) отсутствие эффекта 30% (3/10) CR 20% (2/10) PR 50% (5/10) no effect 30% (3/10)	8-31

Авторы Authors	Количество очагов/ пациентов No. of lesions/ No. of patients	Фотосенсибилизатор Photosensitizer	Режим облучения Irradiation mode	Световая доза, Дж/см² Light dose, J/cm²	Количество курсов ФДТ Number of PDT courses	Тип очага Type of lesion	Результат терапии, % пациентов Results of therapy, % of patients	Срок наблюдения, мес Follow-up period, month
Quéreux и соавт., 2013 [40]	29/12	Метиловый эфир 5-АЛК 5-ALA methyl ester	Лазер, 630 нм Laser, 630 nm	37	2-6	20 пятен 9 бляшек 20 patches 9 plaques	ПР 50% (6/12) ЧР 25% (3/12) отсутствие эффекта 25% (3/12) CR 50% (6/12) PR 25% (3/12) no effect 25% (3/12)	6-35
Kaufmann и соавт., 2017 [16]	1/1	Метиловый эфир 5-АЛК 5-ALA methyl ester	Светодиод, 630 нм LED, 630 nm	Не указана Not specified	8	Пятно Patche	ПР 100% CR 100%	48
Pileri и соавт., 2017 [41]	4/4	Метиловый эфир 5-АЛК 5-ALA methyl ester	Диодная лампа, 630 нм LED lamp, 630 nm	37	4-9	Пятна Patches	ПР 50% (2/4) ЧР 50% (2/4) CR 50% (2/4) PR 50% (2/4)	6-120
Jang и соавт., 2018 [43]	2/2	Метиловый эфир 5-АЛК 5-ALA methyl ester	Светодиод, 630 нм LED, 630 nm	37,5	2	Пятна Patches	ПР 100%	47-87

Примечания: ПР – полная регрессия, ЧР – частичная регрессия.
Note: CR – complete regression, PR – partial regression.

Conclusion

The main advantages of PDT in patients with MF include the absence of systemic toxicity, non-invasiveness, selectivity of action, the absence of carcinogenic potential, the possibility of conducting several courses of treatment, and good cosmetic results. PDT shows high efficiency in patients with isolated or limited spots and plaques. PDT can be considered as the therapy of choice in patients with facial lesions where a good cosmetic result is one of the main requirements, while radiation therapy, nitrogen mustard or carmustine can leave permanent and visible scars. Plaques located in the axillary or inguinal folds of the skin, which are inaccessible to phototherapy, can also be treated with PDT [6].

Studies show that several courses of PDT are usually required to treat patients with MF, although the exact frequency of courses remains uncertain. Most of the authors conducted courses every 2-4 weeks with a frequency that allows removing crusts before the next course. The total number of courses depends on the clinical response and varies significantly in the studies of different authors (range from 2 to 11 courses) [16, 17, 27-29, 31-43]. According to M. Fernández-Guarino et al. in the absence of a response to PDT, 6 courses may be considered sufficient before interrupting treatment and considering other therapy options [6].

Treatment failure in patients with large plaques has been reported in some cases, and therefore the authors do not recommend PDT for lesions greater than 7.5 cm in diameter [6]. Other clinical studies show that the effectiveness of PDT does not depend on the size of the lesion, but may be related to the number of lesions, the thickness of the stratum corneum, the tumor cells infiltration degree, and the depth of invasion [17].

Despite a small number of studies and the absence of clear recommendations on PDT regimens in patients with MF, PDT is an effective and promising treatment for these patients.

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