

## The combined therapy «PUVA + interferon- $\alpha$ » in cutaneous T-cell lymphoma treatment

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**Key words:** cutaneous T-cell lymphoma, interferon- $\alpha$ , mycosis fungoides, PUVA

### Introduction

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of neoplastic diseases caused by the proliferation of the lymphocytes' clone in the skin that shows considerable variation in clinical presentation, histologic appearance, immunophenotype and prognosis. CTCL represents more than 65% of all primary cutaneous lymphomas. Cutaneous lymphomas make 2% of all dermatological diseases. For quite a long time only two types of CTCL had been known: Mycosis fungoides and Sezary syndrome. Many years had passed before the researchers identified new species of CTCL via clinical and immunophenotypic criteria analysis. Usually CTCL begins at an old age, although it can affect younger people and even children. CTCL is more common in men than in women (2:1). Besides, in the U.S. CTCL is more common among African Americans than among white citizens. A great increase of the CTCL incidence has been fixed worldwide lately: 3% per year only in the U.S. and E.U.-countries.

The concrete cause of CTCL is unknown.

According to the researches lymphocytes become malignant due to changes of the DNA genetic code as a result of the factors increasing risk of the disease development, initiating oncogenic mutations and promoting appearance of malignant T-lymphocyte clone. These factors may be Epstein-Barr virus, human T-lymphotropic virus – HTLV-1, HTLV-2, human herpesvirus 6 (HHV-6) and Borrelia burgdorferi, chemicals (including medicines), the ionizing radiation, even in small doses. The most common type of CTCL is mycosis fungoides (MF).

Mycosis fungoides makes 75% of all CTCL cases. Mostly it arises among men at the age of 40-60 and develops slowly within decades. It is generally accepted to allocate 3 stages of classical form of MF:

1 stage (spotty) is presented with single or multiple shelled spots up to 10-20 cm in diameter, which may be located on any site of cutaneous integument looking like eczematous centers or parapsoriasis plaque. Rashes can exist for years. At the same time their spontaneous regress is also possible. Patients are disturbed by an intense itching. It is quite hard to establish the correct diagnosis at this stage. 5 years or more usually pass since the beginning of the disease till the statement of the correct diagnosis. Patients can be considered to have atopic dermatitis, psoriasis, seborrheic dermatitis. However persistent itching and resistance to the applied therapy help to state the clinical diagnosis of MF.

2 stage (plaque) is characterized by transformation of spots into sharply delimited, intensely itching flat infiltrative reddish-bluish plaques of various degree of density and rising over the skin level or their appearance on visibly healthy skin. The elements can spontaneously regress or merging together they can form large intensely itching centers with clear boundaries due to the center regress. On a surface of some plaques peeling is noted. Rather often it resembles psoriasis. Hyperkeratosis of palms and feet, onychomycosis are an often case. Alopecia develops at affection of the scalp.

3 stage (tumoral) is characterized by domed brownish-red nodes with a smooth surface. There are some frequent places of their appearance: face, neck, skin of axillary, inguinal and femoral folds. Active growth and collapse of the nodes resulting in deep ulcers with the bloody and purulent discharge form are natural for this stage as well. The intense itching, fatigue, appetite loss and body temperature increase are subjectively noted. Lymph nodes and internal organs (lungs, a liver, a spleen) are affected at final stages. The marrow is affected quite rarely.

Erythrodermic variant of mycosis fungoides

In most cases erythroderma develops sharply and spreads through the skin without any previous rashes. However a long-term period of skin rash may precede the erythroderma. These elements can spread and merge together which leads to the development of partial or full erythroderma. The affected skin becomes infiltrated red with a purple shade; a peeling may appear. Sometimes the skin becomes ashy and brown (melanodermic variant). Patients complain of intolerable itch, burning and swollen skin, shivering. And also sweat secretion disorder, total alopecia, onychodystrophy, hyperkeratosis of palms and feet, the peripheral lymph nodes growth and cachexia are observed.

Mycosis fungoides lasts for ages or even decades. At tumoral stage with throughout spreaded disease and internal organs affected the prognosis is poor. MF may transform into the large-cell cutaneous lymphoma with an aggressive clinical behavior. The life expectancy of such patients doesn't exceed 3 years.

Nowadays the treatment of CTCL which depends on the stage of the disease makes great difficulties for the clinicians. They use corticosteroids (prednisolone, triamcinolone, dexamethasone, metypred), chemotherapy using cytotoxic drugs of different groups: alkylating (prospidinum, spirobrominum, cyclophosphan), antimetabolites (methotrexate, 6-mercaptopurine), organic alkaloids (vinblastine, vincristine), antitumor antibiotics (adriamycin, bleomycin), interferon-therapy, which is able to restore the antitumor protecting mechanisms, radiation therapy and retinoids.

Perfect results were obtained by application of PUVA-therapy. Recently the combination of PUVA and antiviral drugs is commonly used. However there are no published data on this matter.

**Aim**

The exploration of the effectiveness of combined therapy: PUVA via antiviral drugs in CTCL-patients treatment.

**Materials and methods**

This clinical research was conducted at V.A. Rakhmanov Department of Skin and Sexually-Transmitted Diseases (the First Moscow State Medical University, Russia) and the Hematology Science Center (Moscow, Russia). We observed 8 patients with CTCL: 3 (37.5%) men and 5 (62.5%) women at the age of 50-56. The diagnoses were verified with histological, immunohistochemical and clonal hematological research methods. The duration of the disease ranged from 2 to 36 years. The patients had different stages of the CTCL: IA – 3 patients, IB – two patients, IIA – one patient, IIB – one patient. Before the treatment all the patients were fully examined; the contraindications for photochemotherapy were not revealed. The Hematology Science Center prescribed Reaferon (3 million units – 3 times per week). At the same time the photochemotherapy based on skin exposure with UV (wavelength 320-400 nm) in 2 hours after ammifurin intake (photosensitizer) was applied in our clinic. The initial dose of the irradiation depended on the phototype of the patient's skin and was 0.5-1.0 J/cm<sup>2</sup>. Photochemotherapy was carried out 4 times a week with gradually increasing dose of 0.5-1.0 J/cm<sup>2</sup> in every 2 sessions to a single dose of 8-10 J/cm<sup>2</sup>. The course of therapy consisted of 20-30 procedures.

**Results**

After the combined therapy we reached the clinical remission in 75% of cases. The clinical behaviour was improved in 25% of cases (reduction and cessation of itching, blanching and flatter of lesions). At IA-IIA stage of CTCL the treatment was noted to be more effective.

**Conclusion**

Thus, basing on the results of our research, we can maintain that nowadays the photochemotherapy in combination with interferon- $\alpha$  is one of the most effective methods of CTCL-treatment, which can be recommended to practical doctors.