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Efficacy of brentuximab vedotin in patients with CD30-positive lymphoproliferative skin diseases: results of the first prospective study in the Russian Federation

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Background. Primary cutaneous lymphomas are the second most common group of extranodal lymphomas. Unlike nodal lymphomas, which are characterized by predominant B-cell proliferation, primary cutaneous T-cell lymphomas account for 65–75% of all cutaneous lymphomas. About 50% of all cutaneous T-cell lymphomas are mycosis fungoides (MF). CD30-positive lymphoproliferative disorders (CD30+ LPD) occupy the second place in the incidence of cutaneous T-cell lymphomas, while 10% are rare disease forms such as primary cutaneous peripheral T-cell lymphoma not otherwise specified (PTL–NOS), Sézary syndrome (SS), etc.
Treatment of MF/SS patients in the Russian Federation shows that about 30% of individuals are resistant to various therapeutic effects, especially in the later stages. The problem of CD30+ LPD treatment is extracutaneous dissemination in the case of primary cutaneous anaplastic large cell lymphoma (pcALCL) and steadily relapsing lymphomatoid papulosis (LyP) without symptom-free intervals. These aspects of the therapy of cutaneous lymphomas highlight the need to search for new treatment options.
According to the results of the international randomized ALCANZA trial, brentuximab vedotin (BV) has shown high efficiency in the treatment of cutaneous T-cell lymphoproliferative disorders.
Study objective. The study aim is to evaluate BV efficacy in the group of poor prognosis patients with cutaneous T-cell lymphomas who has received at least one line of systemic therapy.
Materials and methods. The study included 21 patients: 16 men and 5 women. There were 8 patients with MF, 5 patients with SS; 6 individuals had cutaneous CD30+ LPD (including 5 patients with pcALCL and 1 individual with LyP) and 2 patients were diagnosed with PTL–NOS. Cutaneous T-cell lymphoma was confirmed based on the medical history, nature of cutaneous lesions, as well as histological, immunohistochemical, and, in some cases, molecular genetic testing of the skin biopsy sample (analysis of T-cell receptor gene rearrangement).
Results. Late stages of the disease were diagnosed in 12 out of 13 patients with MF/SS. Extracutaneous lesions were diagnosed in 57% of cases. The median of prior lines of therapy was 3 (1–8 variants of treatment). The overall response to the treatment was achieved in 91% of cases (19 out of 21 patients): complete remission was observed in 53% of patients, very good partial remission was achieved in 31% of individuals, and partial remission was noted in 16% of cases. Disease progression was found in 2 patients (after cycles 1 and 4). Some patients with partial remission after BV therapy underwent additional therapy (radiation therapy, interferon α therapy, and cycles of systemic therapy), which made it possible to achieve a more pronounced antitumor response. Early relapse was diagnosed in 2 out of 19 patients who had responded to the treatment. The treatment tolerability was acceptable, and the toxicity did not exceed that described in the previous studies. Thus, the overall stable antitumor response persisted in 89% of patients (the median follow-up was 10 months).
Conclusion. The use of targeted therapy with BV made it possible to achieve high treatment results in patients with advanced stages of the disease and the absence of response to several lines of therapy.

Keywords: **primary cutaneous T-cell lymphomas, targeted therapy, brentuximab vedotin, mycosis fungoides, lymphomatoid papulosis.**

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Background

Primary cutaneous lymphomas are the second most common group of extranodal lymphomas. Unlike nodal lymphomas, which are characterized by predominant B-cell proliferation, primary cutaneous T-cell lymphomas account for 65–75% of all cutaneous lymphomas with an average incidence of about 10.2 million per population per year [1]. The European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO) developed a consensus classification of cutaneous lymphomas in 2005 [2], which was updated in 2019 [3]. About 50% of all cutaneous T-cell lymphomas are mycosis fungoides (MF), which is one of the most common skin lymphomas. CD30-positive lymphoproliferative disorders (CD30+ LPD) occupy the second place in the incidence of cutaneous T-cell lymphomas, while 10% of the latter are rare disease forms such as primary cutaneous peripheral T-cell lymphoma not otherwise specified (PTL–NOS), Sézary syndrome (SS), etc. MF is a primary epidermotropic cutaneous T-cell lymphoma characterized by a slow gradual progression of macules, plaques, nodules, and an epidermotropic (adnexotropic) infiltrate predominantly composed of small to medium-sized lymphoid cells with round or cerebriform nuclei and an effector memory phenotype. Its diagnosis is based on a combination of clinical and anamnestic data, histological and immunohistochemical studies, and determination of clonality for genes of the gamma and beta chains of the T-cell receptor in a skin biopsy sample [4].

Primary cutaneous CD30+ lymphomas include two diseases: lymphomatoid papulosis (LyP) and primary cutaneous CD30+ anaplastic large cell lymphoma (pcALCL). LyP is characterized by recurrent lesions of spontaneously resolving multiple nodules, proliferation of atypical CD30+ lymphoid cells, and a favorable prognosis with no effect on survival. In 20% of cases, LyP is associated with the development of other lymphoproliferative diseases (mycosis fungoides, cutaneous anaplastic lymphoma, and lymphogranulomatosis) [3]. However, LyP treatment does not reduce the risk of developing secondary tumors [4]. pcALCL is characterized by rapidly developing, often large (≥2 cm) and solitary nodules, proliferation of large atypical CD30+ lymphoid cells, a relatively favorable prognosis with spontaneous remission in 20–40% of cases, followed by frequent recurrence. Extracutaneous MF, predominantly to regional lymph nodes, occurs in 10% of cases [5].

The strategy for treating patients with cutaneous T-cell lymphomas depends on disease stage [6]. According to the TNM classification system for MF/SS, four clinical stages of MF are conventionally divided into early (IA–IIA) and late (IIB–IVB) stages. Topical therapy is used to treat early stages; it includes the use topical corticosteroids (TCS), photo- and radiotherapy. The role of topical therapy in preventing the progression of advanced cutaneous T-cell lymphomas is not fully understood; this therapy is used mainly as a palliative approach aimed at improving the quality of life of patients [7]. Currently, there are no specific algorithms to treat early stages of the disease; treatment should be selected according to individual patient's characteristics and the profile of side effects. Zackheim et al. published a large prospective study in 79 patients with T1 and T2 MF, most of whom used class 1 TCS usually twice daily. Complete remission was achieved in 63% of cases, partial remission was noted in 31% of patients, while the overall response rate was 94% in the T1 group and 25%, 57%, and 82% in the T2 group. After discontinuation of TCS therapy, only 37% of T1 patients and 18% of T2 patients remained in complete remission during a mean follow-up period of 9 months [8].

Phototherapy traditionally includes narrowband ultraviolet B (UVB) radiation and PUVA therapy. Phototherapy is used as either monotherapy or in combination with systemic therapy. In most cases, it proves to be efficient and superior to the effect of systemic drugs. There is a consensus in the literature that narrowband UVB is less effective in transient remission than PUVA, especially in thicker plaques. However, there are few comparative studies. A retrospective study of 95 patients with early-stage MF (IA, IB, and IIA) receiving PUVA therapy and 19 patients treated with UVB showed that UVB was as effective as PUVA with comparable rates of complete remission in 62.1% and 68.4% cases and no significant difference in the time to relapse after 11.5 and 14 months of PUVA and UVB treatment, respectively [9].

According to the Russian guidelines for the treatment of cutaneous T-cell lymphomas, radiotherapy is used in all MF stages F [4]. Local radiotherapy is more commonly used in plaques and nodules; it can be carried out in combination with other therapies, including phototherapy, other topical therapies, or in combination with systemic therapy. Total skin electron beam therapy (TSEBT) is performed in patients with generalized rash and erythroderma. The consensus recommendations for radiotherapy were published by the International Lymphoma Radiation Oncology Group in 2015 [10]. Late MF stages usually require the use of systemic therapies.

Treatment of CD30+ LPD is focused on the number and distribution of skin rash. Therapy options include surgical resection, local radiotherapy, use of low-dose methotrexate, narrowband UVB, PUVA therapy, and administration of topical glucocorticosteroids [11]. There is no evidence of the superiority of any of these therapies: the response rates for PUVA therapy and methotrexate treatment are 56% and 57%–88%, respectively [12, 13].

Thus, treatment of MF/SS patients in the Russian Federation shows that about 30% of individuals are resistant to various therapeutic effects, especially in the later stages. The problem of LyP/pcALCL treatment is extracutaneous dissemination in pcALCL and steadily relapsing LyP course without symptom-free intervals. These aspects of the therapy of cutaneous lymphomas highlight the need to search for new treatment options.

Study objective: to evaluate the efficacy of brentuximab vedotin in the group of poor prognosis patients with cutaneous T-cell lymphomas who has received at least one line of systemic therapy.

Materials and methods

The study included 21 patients who were observed and treated with specific therapy at several Russian medical institutions [14]. There were 16 males (median age, 52 years) and 5 females (median age, 62 years). Eight patients were diagnosed with MF; there were 5 individuals with SS, 6 patients with cutaneous CD30+ LPD (5 cases of ALK-negative pcALCL and one case of LyP), and 2 individuals with PTL–NOS. One patient was diagnosed with LyP associated with MF and pcALCL.

The diagnosis of cutaneous T-cell lymphoma was confirmed based on the medical history, nature of cutaneous lesions, as well as histological, immunohistochemical, and, in some cases, molecular genetic testing of the skin biopsy

sample (analysis of T-cell receptor gene rearrangement). In all cases, immunohistochemical study with the CD30 antigen and quantitative assessment of CD30+ tumor cells were carried out for all cells of the infiltrate.

The staging of MF and SS was conducted according to the recommendations of the International Society for Cutaneous Lymphomas and EORTC for MF and SS (ISCL–EORTC). In addition to standard examinations, if necessary, a PET/CT study was performed to assess extracutaneous generalization of the process in detail.

The response to treatment is determined according to the criteria proposed by ISCL, EORTC, and the United States Cutaneous Lymphoma Consortium (USCLC) [15].

1. Skin (T):

– complete remission (CR): 100% disappearance of skin lesions;

– partial remission (PR): 50–99% resolution of skin lesions (decrease in volume) of the baseline level, the absence of new nodules (T3) in T1, T2, and T4 stage patients;

– stable disease: from an increase in skin lesions (volume) by < 25% to resolution of lesions by < 50% compared to the baseline, absence of new nodules (T3) in T1, T2, and T4 stage patients;

– progressive disease: an increase in skin lesions (volume) by > 25% of the baseline level, occurence of new nodes (T3) in T1, T2, and T4 stage patients, or no response (an increase in rash by 50% of the baseline in patients with CR and PR;

– relapse: development of skin rash in patients with CR.

2. Lymph nodes (N):

– complete remission (CR): all lymph nodes are either ≤ 1.5 cm at the largest diameter (longest axis) or histologically negative; N3 lymph nodes ≤ 1.5 cm at the largest diameter and > 1 cm at the smallest diameter are ≤ 1.0 cm at the smallest diameter or histologically negative;

– partial remission (PR): a cumulative decrease of ≥ 50% in the sum of length products (SLP), which is the sum of the products of "the maximum longitudinal length × the maximum transverse length" of each affected lymph node and the absence of new lymph nodes > 1.5 cm in diameter along the longest axis or > 1 cm along the shortest axis;

– stable disease: absence of criteria for CR, PR and disease progression;

– progressive disease: increase in SLP by ≥ 50% of the baseline, occurrence of a new lymph node > 1.5 cm in diameter along the longest axis or > 1 cm along the shortest axis, or no response: increase in SLP by > 50% of the maximum effect in patients with CR;

– relapse: development of new histologically confirmed N3 lymph nodes > 1.5 cm at the largest diameter.

3. Visceral organs (M):

– complete remission (CR): no organ enlargement during physical examination and no pathological CT changes (biopsy of any new lesions occurring after treatment to rule out lymphoma);

– partial remission (PR): < 50% regression of lesions in the liver, spleen, or other initially affected organs with the possibility to measure lesion volume (SLP), no enlargement of the organ in size and involvement of new organs;

– stable disease: absence of criteria for CR, PR and disease progression;

– progressive disease: > 50% increase in organ size, damage to the new organ, or no response: > 50% increase in SLP of the maximum effect in patients with PR;

– relapse: involvement of a new organ in patients with complete remission.

4. Peripheral blood (B):

– complete remission (CR): B0;

– partial remission (PR): a decrease in quantitative parameters of blood damage by > 50% of the baseline level in B2 stage patients;

– stable disease: absence of criteria for CR, PR and disease progression;

– progressive disease: transition from stage B0 to stage B2 or an increase in the number of tumor cells by > 50% of the baseline (5,000 cells per 1 μl);

– relapse: increase in the level of tumor lymphocytes in the blood of patients with CR>B1.

In addition, a new criterion for response to therapy was introduced in this study: a very good PR, which stands for the following:

1. skin (T): ≥75% resolution of lesions or reduction in skin lesion size compared to the baseline, absence of new nodules (T3) in T1, T2, and T4 stage patients, and response duration of ≥ 4 months;

2. lymph nodes (N): a cumulative decrease of ≥ 75% and the absence of new lymph nodes > 1.5 cm in diameter along the longest axis or > 1 cm along the shortest axis, and response duration of ≥ 4 months;

3. visceral organs (M): ~75% regression of lesions in the liver, spleen, or other initially affected organs with the possibility to measure lesion volume (SLP), no enlargement of the organ and involvement of new organs, and response duration of ≥ 4 months;

4. peripheral blood (B): a decrease in quantitative parameters of blood damage by > 75% of the baseline level in B2 stage patients and response duration of ≥ 4 months;

The presence and level of brentuximab vedotin (BV)-induced neuropathy were assessed in patients available for the follow-up according to the proposed criteria for the analysis of peripheral neurotoxicity [16,17].

A retrospective and prospective analysis for evaluation of response to BV treatment in patients with different forms of cutaneous T-cell lymphomas was carried out.

Results

The study included 21 patients. The majority of MF/SS patients had late stages of the disease (IIB–IVB): 10 out of 13 patients (Fig. 1a, b; Fig. 3). Two patients were diagnosed with MF transformation to large cell lymphoma, and only one patient had the IA stage. Among cutaneous lymphomas other than MF/SS, the volume of skin lesions was T2–T3 in 75% of cases (multiple rashes limited to one or several regions). Extracutaneous lesions (involvement of lymph nodes, internal organs, and the peripheral blood) were diagnosed in 57% of individuals (12 out of 21 patients). In all patients, the number of CD30+ cells was at least 5% of all cells in the infiltrate.

All patients underwent several lines of therapy before the start of targeted therapy. Thus, the median of prior line of therapy was 3 (1–8 variants of treatment). The therapy is ongoing in six patients at the time of publication.

The number of BV cycles ranged from 1 to 18 (median, 7 injections).

The overall response to treatment was achieved in 91% (19 out of 21 patients). Of these, 53% achieved CR (Fig. 2a, b; Fig. 4), while 31% and 16% had a very good PR and PR, respectively. Progressive disease was noted in 2 patients (after cycles 1 and 4).

We evaluated the antitumor response rate and noted that, in MF/SS patients, the response was usually achieved more slowly and gradually, from cycle to cycle, on average not earlier than after cycle 4.

In some patients who achieved PR as a result of BV administration, additional therapy was performed. This treatment included radiotherapy against residual lesions, TSEBT, immunotherapy with interferon alfa, and courses of systemic CHOP treatment, which made it possible to achieve a more pronounced antitumor effect.

Of 19 patients who responded to treatment, 2 individuals were diagnosed with early relapse occurring in the period of up to 6 months of follow-up after the stop-therapy.

Ten patients were available for evaluation of BV-induced peripheral neuropathy. Of them, 3 patients developed clinically insignificant neuropathy (stage I) and 1 individual developed clinically significant neuropathy (stage III) that required dose reduction. Three patients complained of weakness and fatigue after drug administration.

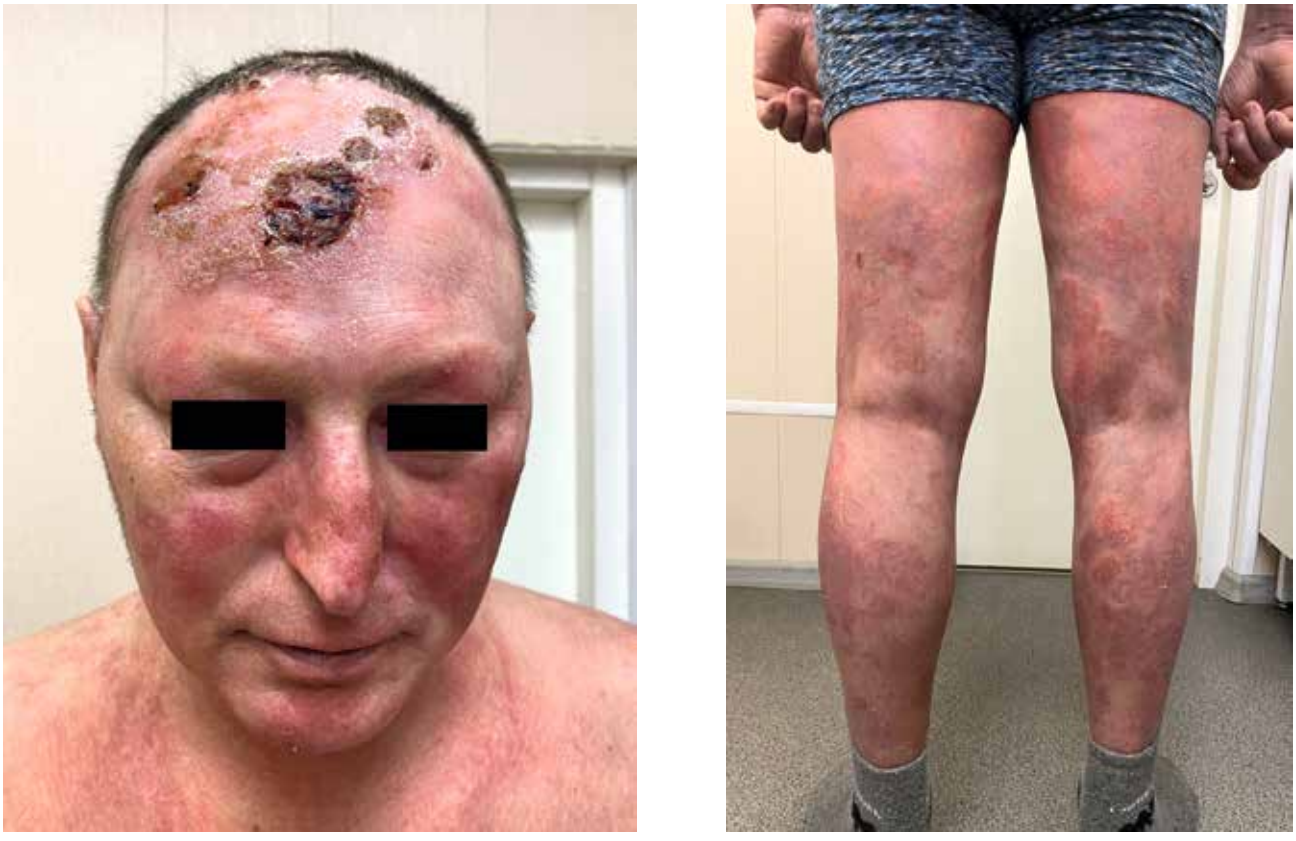
Thus, 89% of patients maintained a stable overall antitumor response with a median follow-up of 10 months.

Discussion

The safety and efficacy of BV, a monoclonal anti-CD30 antibody conjugated to monomethyl auristatin E, in cutaneous lymphomas was evaluated in the first part of Phase II study in patients with LyP/pcALCL and MF/SS. The overall response was 73% with complete remission rate of 35%. The response rate was 100% in the LyP/pcALCL group and 54% in the MF/SS group, with the median duration of response being longer in the latter [18]. The second part of Phase II study included evaluation of BV efficacy in MF/SS patients with different CD30 expression levels. Median CD30 expression was 13%; 14 patients (44%) had a CD30 level of < 10%. The overall response rate was 70%, with median CD30 expression being higher in the responders compared to the non-responder group [19]. It should be noted that similar studies in the group of nodal T-cell lymphomas have showed that sensitivity to BV occurs when at least 1% of tumor cells express the CD30 antigen.

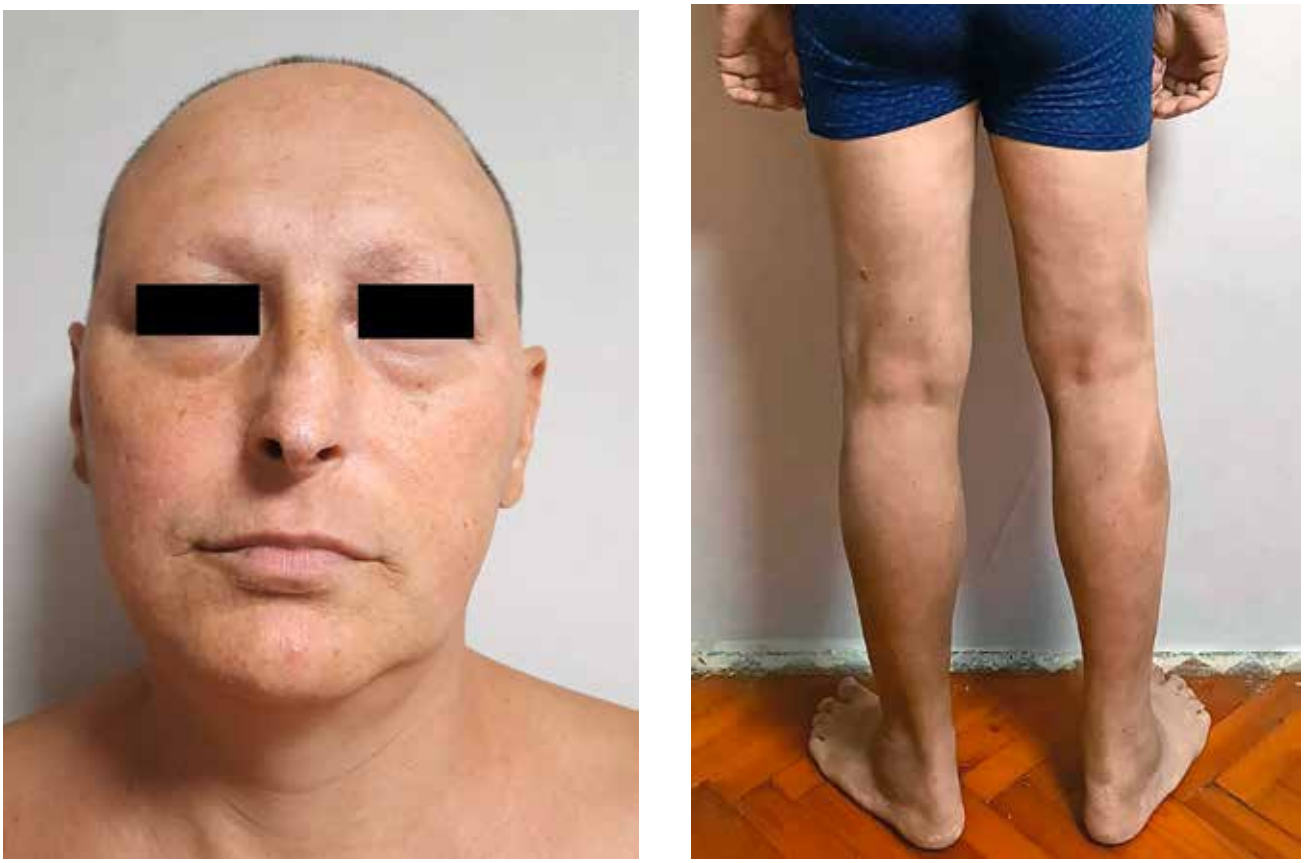
Based on such positive results of both parts of Phase II study, the international randomized ALCANZA trial was initiated to compare two therapy lines: treatment with BV and physician's choice (methotrexate/bexarotene). It was shown that the use of BV has significant advantages over methotrexate/bexarotene in terms of overall response rate, duration of 4 months, and median event-free survival: 56.3% versus 12.5% and 16.7 versus 3.5 months, respectively [20]. The most common and adverse side effect was the development of peripheral polyneuropathy (67% of patients). However, clinical symptoms regressed in 86% of patients with a decrease in dose and during the follow-up after the end of treatment.

Studies on the efficacy of BV used in combination with other chemotherapy drugs, as well as neurotoxicity



a *b*

Fig. 1. A 45-year-old patient with stage IIB mycosis fungoides (T3N0B0M0) prior to brentuximab vedotin therapy. The patient had the disease for 8 years, underwent courses of photo- and radiotherapy, treatment with vorinostat and methotrexate with transient partial remissions. Tumors on the forehead and scalp, confluent patches and plaques on the skin of the face (*a*). Widespread patches and plaques on the skin of the lower extremities (*b*)



a *b*

Fig. 2. A 45-year-old patient with IIB stage mycosis fungoides (T3N0B0M0) after 7 injections of brentuximab vedotin. Complete remission (*a*, *b*)

reduction in cutaneous lymphomas, are currently ongoing (NCT02616965 BV + romidepsin, NCT03587844 BV at doses of 0.9–1.2 mg/kg).

In the present study, the median age of patients with CD30+ lymphoproliferative diseases was 57 years; all patients received multiple lines of therapy prior to initiation of BV treatment (median, 3; range, 1–8 lines of therapy). BV was administered at a standard dose of 1.8 mg/kg daily for 21 days. Treatment duration was 1–18 cycles. The overall response to treatment is 91%; the rates of complete, very good partial, and partial remissions (53, 31, and 16%, respectively) were higher in our study compared to previous works [18, 19]. This can be due to a smaller number of prior therapy lines received by our patients and heterogeneity of lymphomas included in the study (8 patients with MF, 5 individuals with SS, 5 cases of pcALCL, 1 patient with LyP, and 2 individuals with PTL–NOS). Except for clinical trials, literature data on the treatment of cutaneous lymphomas with BV are limited mainly to case reports and small literature reviews. For instance, Enos et al. analyzed the results of BV treatment in patients with large cell transformation of MF and pcALCL [21]. The study included 61 patients with CD30+ large cell transformation of MF and 7 patients with pcALCL. The overall treatment response was achieved in 67.7% of cases. Of these, complete remission of the disease was noted in 16.2% of patients (100% for pcALCL and 6.6% for MF groups). The median response time was 5.3 and 9.3 weeks for pcALCL and MF, respectively. The mean response duration was 7.6 and 7.8 months for pcALCL and MF, respectively. Peripheral neuropathy (57.2%) and fatigue (35.6%) were the most frequently observed side effects.

In our study, we did not manage to reliably assess the presence and incidence of BV side effects in all patients for several reasons. Firstly, some patients were available only based on medical records obtained at the time of short-term hospitalizations for drug administration. Secondly, several patients were lost for the follow-up. Of 10 patients available for analysis, 4 individuals had signs of peripheral neuropathy and 3 patients complained of fatigue and weakness after drug administration.

In this study, we considered it necessary to introduce a new criterion of treatment response: “very good partial remission”. The term implies 100% resolution of skin rash. Resolution of all rash is often visually observed in patients after treatment. However, patients do not consider it complete remission during the survey, since they still have subjective complaints of xerosis and discomfort, peeling, and post-inflammatory hyper- or hypopigmentation. Taking into account the presence of hypo- and hyperpigmented variants of MF, it is often almost impossible to distinguish post-inflammatory macules from active hypo- or hyperpigmented lesions. In these case, we suggest using the term “very good partial remission”.

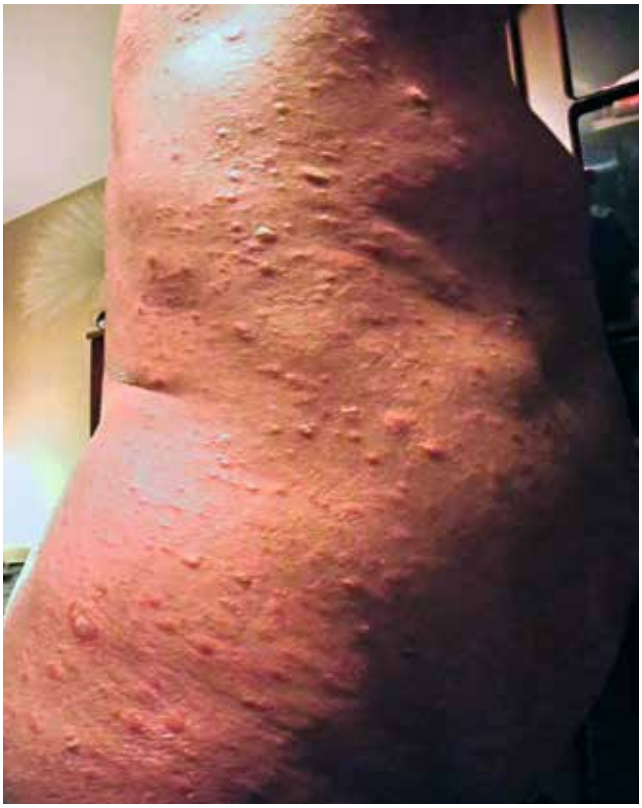


Fig. 3. A 54-year-old patient with Sézary syndrome prior to brentuximab vedotin therapy. The patient had the disease for 7 years, underwent total skin electron beam therapy and treatment with interferon and vorinostat with no significant effect. Small disseminated plaques and papules developed due to erythroderma

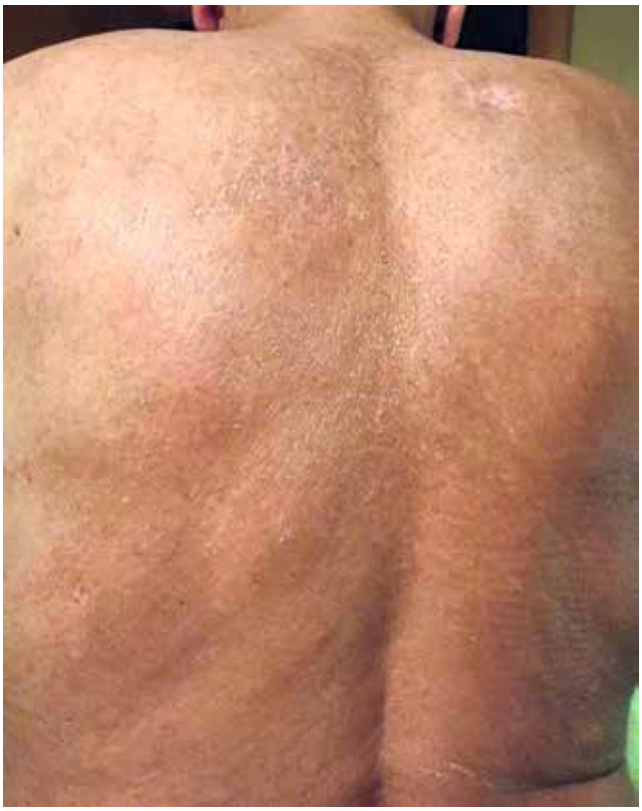


Fig. 4. A 54-year-old patient with Sézary syndrome after 6 injections of brentuximab vedotin. Complete remission

BV therapy is performed according to the standard protocol for the treatment of nodal (systemic) lymphomas (dose, 1.8 mg/kg; at least 8 cycles per treatment course). According to official recommendations, dose reduction to 1.2 mg/kg is possible in case of serious side effects. However, the accumulation of experience and patient observation allowed us to conclude that it is possible to use lower doses of BV and reduce the number of injection cycles in cases other then unacceptable drug toxicity, which is confirmed by literature data. Cutaneous lymphomas differ significantly from their systemic analogues in the biological characteristics of the tumor, disease course and prognosis. Observation of patients treated with a lower drug dose at longer intervals showed that they maintain a good response to treatment [22–24].

The incidence of peripheral neuropathy with the use of standard doses of BV is higher in LyP (81%), pcALCL and MF (67%) compared to systemic ALCL (62%) and Hodgkin's lymphoma (61%) [25]. This may be due to the presence of fewer target cells in cutaneous lymphomas for the drug, resulting in increased non-targeted drug delivery and diffusion to peripheral nerves. Thus, regimen with less frequent BV administration may be more appropriate for cutaneous lymphomas, since they may reduce the risk of neuropathy.

The present study showed that BV is an effective and well-tolerated drug for the treatment of advanced CD30+ LPD. The issues of studying and developing a treatment protocol specific for cutaneous lymphomas require further efforts. In particular, optimization of the strategy for either continuing treatment or switching to maintenance therapy after the initial period of drug response evaluation is possible with increasing the number of observations. Questions about the use of BV as the first-line therapy in patients with advanced stages of the disease and the possibility of combined use of BV with chemotherapy drugs, radiation and topical therapy remain open.

Conclusion

The use of brentuximab vedotin in the unfavorable group of pretreated patients with cutaneous T-cell lymphomas has demonstrated quite encouraging treatment results with the possibility of achieving a high overall response rate with acceptable toxicity.

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