

Nivolumab in two cases of refractory mycosis fungoides erythroderma

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Abstract

Mycosis fungoides (MF) is the most common subtype of primary cutaneous T cell lymphoma (CTCL). The erythrodermic form (T4) especially impairs health-related quality of life (HR-QoL), making patients often incapable of self-care. Mycosis fungoides and Sézary syndrome (SS) are immunogenic neoplasms and can be recognized by the patient's immune system. The disease is chronic and immunotherapy allows for long-term control of CTCL. The paper presents a description of 2 cases of nivolumab use in the salvage treatment of erythroderma in the course of refractory mycosis fungoides. Nivolumab was used as emergency treatment, and previously patients exhausted the available treatment options. The discussed cases confirm the effectiveness of immunotherapy in the treatment of primary cutaneous T cell lymphomas. The applied treatment achieved the effect of more than one year of response (15 months), as well as a significant benefit in terms of subjective and objective quality of life. The effect was mainly related to the condition of the skin. The use of the PD-1 checkpoint inhibitor allowed for over 12 months of control in advanced, refractory and heavily pretreated cutaneous lymphoma, and was very well tolerated. More research is needed on the use of such inhibitors in the treatment of cutaneous lymphomas.

Key words: nivolumab, refractory disease, mycosis fungoides erythroderma.

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Introduction

Mycosis fungoides (MF) is the most common subtype of primary cutaneous lymphoma [1]. The erythrodermic form (T4) especially impairs health-related quality of life (HR-QoL), making patients often incapable of self-care [1-3].

The erythrodermic stage usually occurs when treatment in the earlier stages of the disease has failed, but sometimes the lymphoma manifests itself from the first symptoms with erythroderma [1-3]. In the erythrodermic stage, the risk of sepsis increases, which is the result of both bacterial and fungal infection of generalized skin lesions, but also the result of profound damage of the immune system.

Despite the usually indolent course of MF in the erythrodermic phase of the disease, the prognosis is unfavorable [1-3]. According to the recommendations of both NCCN and ESMO guidelines, one of the basic options of first-line treatment is interferon, which acts by activating the immune system's defense [4-6].

Currently, the portfolio of medicaments that show efficacy in MF such as brentuximab vedotin (BV) for CD30 positive lymphomas or mogamulizumab is slowly increasing [7-9], but the treatment of relapsing, heavily pretreated patients is still a significant clinical problem.

In two published clinical trials and in individual published case reports, the efficacy of programmed death receptor (PD-1) inhibitors or cytotoxic T cell antigen 4 (CTLA-4) inhibitors was indicated [9-13].

In the current NCCN recommendations, in case of failure of the previous treatment methods, the use of a PD-1 inhibitor is recommended based on a phase II study [4], although the role of anti PD-1 therapy has not yet been fully defined.

Case 1

In a 64-year-old Caucasian patient, the diagnosis of MF was made in 2009 after many years of treatment of skin lesions diagnosed as atopic dermatitis. Topical therapy and methotrexate were applied. The erythrodermic stage T4N0M0, B2-IV A2 was diagnosed in 2014. The patient was qualified for systemic treatment. The following drugs were used: pegylated liposomal doxorubicin, interferon α , and as part of a clinical trial (NCT01482962) pralatrexate. No more than a partial regression in the appearance of the skin has ever been achieved, without reducing the surface area, but resulting in a subjective improvement in the quality of life and a decrease in the number of cancer

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cells in the peripheral blood. Due to meeting the criteria for B2 (high blood tumor burden), the patient was not qualified for whole skin radiotherapy. The patient's condition remained good despite the stage of the disease. Treatment continued until the study was closed by the sponsor's decision. In the next line of treatment, bexarotene was used, and after the effect was exhausted, gemcitabine. In 2018, because of the increasing number of cancer cells in his blood, the patient was referred for photophoresis, which was performed three times. Photophoresis was stopped due to deterioration of the general condition, diagnosis of sepsis caused by *Streptococcus aureus* and subsequent progression of lymphoma.

In October 2019, after 10 years of treatment (6 lines of systemic therapy), the condition of the patient was poor: ECOG 3, erythroderma covering 100% of the body surface, complete alopecia, hectic fever, severe chills. Lactic acid dehydrogenase (LDH), B2 microglobulin, and C-reactive protein (CRP) were significantly increased. Both in the skin and in the peripheral blood the mixed bacterial flora was Gram positive. Neoplastic cells accounted for 13.4% (B1) of the number of T lymphocytes in cytometry. There were no signs of large cell transformation. PET/CT examination excluded the presence of organ lesions, but confirmed the presence of active nodal lesions in both axillas, the groin and the retroperitoneum. After eradication of the bacterial infection, nivolumab treatment was started in November 2019 at a dose of 100 mg (based on 1.5 mg/kg body weight) every 14 days and until January 2021 – during 15 months of therapy the rhythm was maintained every 14 days. There were no hematological complications or any other side effects. The patient's condition was systematically improving. Until January 2021, the patient received 26 injections of nivolumab. The dose was postponed only twice – in July and October 20 (by 14 days). The cause was a mild papular rash that resolved after the use of steroid therapy at a dose of 4 mg for 7 days. No changes in thyroid function were observed. During the treatment, a significant improvement was achieved: disappearance of erythrodermic features, hair regrowth and an improvement of the general condition, normalization of biochemical results, return to normal life activity.

In January 2021, the PET/CT scans confirmed the progression of nodal lesions, which was noticed during physical examination. Core needle biopsy did not show transformation, either large cell or type of lymphoma. The expression of CD30 in the tumor tissue was confirmed and the patient was qualified for BV treatment. To sum up, the patient received 15 months of nivolumab therapy with complete disappearance of the erythrodermia, without complications despite the previous treatment lines and in spite of poor performance status (PS3) at the beginning. The cytometry image continuously showed a stable number of abnormal cells (B1). The progression concerns only

the lymph nodes above and below the diaphragm, not the skin and the blood.

Case 2

In 2008, a 61-year-old Caucasian woman was diagnosed with *de novo* mycosis. No previous history of skin diseases with a similar clinical picture was noted. The coexistence of rheumatoid arthritis, hypothyroidism and glaucoma strongly influenced her general condition. She was treated for several years only with local therapy. In 2013, the disease progressed to stage IVA2 (T4N0M0, B2). The abnormal subset of T lymphocyte by flow cytometry was 80%. The treatment was started with liposomal doxorubicin, and interferon alfa 2b was used as maintenance therapy. Subsequent lines of therapy were: methotrexate, bexarotene and gemcitabine, cytarabine. Each treatment was poorly tolerated and required dose reduction, especially bexarotene and gemcitabine. In December 2019, after 6 years of treatment (and several lines of systemic treatment), the patient's condition was moderately severe: ECOG 3, erythroderma covering 100% of the body surface, very severe chills; apart from alopecia, striking hyperkeratosis of the nails attracted attention. LDH, B2 microglobulin, and CRP were significantly increased. The symptoms of the disease were accompanied by anemia (8.9 g/dl Hb), leukocytosis and coagulation disorders (dimers 5.36 ng/ml) requiring antithrombotic treatment. Neoplastic cells accounted for 70% of the number of T lymphocytes in the cytometric test. Positron emission tomography/computed tomography (PET/CT) examination excluded the presence of organ lesions, and confirmed the presence of active nodal disease above and below the diaphragm, as well as generalized skin infiltration. Nivolumab treatment was started in December 2019 at a dose of 100 mg every 14 days (based on the body weight, a dose of 2 mg/kg), and by January 2021, 25 injections of nivolumab had been administered. Each subsequent injection in the initial phase of treatment was associated with an improvement in the patient's condition, including subjective assessment of the quality of life. Blood morphology has normalized both in terms of the red blood cell picture and hemoglobin level (currently 11.9 g/dl), and the number of white blood cells (WBC; decrease from 16 g/l to 10 g/l). The use of thromboembolism prophylaxis and substitution thyroid hormones was still needed. During the immunotherapy in the dose of 100 mg every 14 days, there was no need to change the dose substituting hypothyroidism. Treatment was given at the planned rhythm without delay.

A significant improvement in the general condition was achieved within 14 months of treatment, despite the coexistence of rheumatic disease. The patient was able to self-care, resulting in ECOG 2, throughout the treatment. Nivolumab treatment ended in January 2021 because of

sudden deterioration including high fever. Antibiotic therapy was effective although the pathogens were not found.

Taking into account the fact of treatment throughout 2020, it is important to note that none of them, despite the SARS-CoV-2 pandemic, was infected with the virus during immunotherapy. They were not vaccinated. The administration of the drug was associated with the arrival at the Cancer Center, a visit to the doctor and administration of the drug – the total time spent in the facility, protected only with a surgical mask, was approximately 4 hours every 14 days.

Comments

Mycosis fungoides and Sézary syndrome (SS) are immunogenic neoplasms and can be recognized by the patient's immune system. The disease is chronic and immunotherapy allows for long-term control of cutaneous T cell lymphoma (CTCL) [12]. The discussed cases confirm the effectiveness of immunotherapy in the treatment of CTCL [9-14]. The effect was mainly related to the condition of the skin – the symptoms of erythroderma disappeared, which resulted in a significant improvement in the general condition and an improvement in the patient's perception of the disease. In the management of patients with cutaneous lymphomas, the importance of accepting one's quality of life is an element of therapy's effectiveness assessment [15, 16]. The applied treatment achieved the effect of not only more than one year of response to treatment (15 months), but also a significant benefit in terms of subjective and objective quality of life. The response time obtained is consistent with the results published by Khodadoust [11], where the median progression-free survival was 12 months, and the data on clinical characteristics are similar, for example in the context of previous lines of treatment. Based on these results, the latest NCCN recommendations [4] indicate the possibility of using pembrolizumab in the treatment of mycosis fungoides and SS in refractory/recurrent disease. Another PD-1 checkpoint inhibitor with a similar mechanism of action is nivolumab. In the phase I study published by Lesokhin, nivolumab was used in various subtypes of lymphomas and its activity was confirmed in, among others, primary T-cell skin lymphomas [10].

Due to the small number of publications relating to immunotherapy of cutaneous lymphomas, there are no data comparing both checkpoint inhibitors in this disease; however, in studies of other cancers, in real-world studies there is no difference between pembrolizumab and nivolumab in terms of overall survival and response to treatment [17]. The first patient returned to normal life activity, and the skin regained its typical appearance and functions, without any signs of stigmatization by the disease. The second one regained the ability of self-care, ceased to be completely dependent on the family and was able to self-medicate.

No previous treatment resulted in such a marked improvement in both patients. What is particularly worth emphasizing is the excellent tolerance of treatment, despite the fact that these are patients treated earlier with many types of treatment and burdened with cumulative toxicity. The direct infusion tolerance was not associated with any complications. This good treatment tolerance is confirmed by the analysis presented at this year's ESMO Conference, which showed that immunotherapy is the best tolerated from all types of systemic treatment [15]. It should be emphasized that nivolumab was used as emergency treatment, and previously patients exhausted the available treatment options. Reports on the use of PD-1 inhibitors in the treatment of MF are case reports, rarely published [12].

The dose of nivolumab used in our patients was adapted to their condition and risk of adverse events. Currently, it is recommended to use a dose of 240 mg every 14 days; the previously standard dose was 3 mg/kg. However, a reduced dose was used. According to Onizuka's [18] and Sehgal's [19] works, the reduced dose is proven to be as effective, while increasing the safety of the treatment by decreased toxicity. This allows for excellent tolerance in heavily burdened patients while maintaining the effectiveness of the procedure.

In salvage treatment, after many lines, in everyday clinical practice, we often reduce the initial dose so as not to expose patients to complications that could be dangerous for them in such a situation. In addition, recent reports from studies analyzing the impact of the pandemic on treatment, including immunotherapy, have shown that anti PD-1 effectiveness is not affected by a reduced dose or increased time intervals [19].

The use of the PD-1 checkpoint inhibitor allowed for over 12 months of control in advanced, refractory and heavily pretreated cutaneous lymphoma, and was very well tolerated. More research is needed on the use of such inhibitors in the treatment of cutaneous lymphomas.

The author declares no conflict of interest.

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