PEGYLATED LIPOSOMAL ENCAPSULATED DOXORUBICIN AND BRENTUXIMAB VEDOTIN IN STAGE IIB MYCOSIS FUNGOIDES – A CASE REPORT

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Abstract

Mycosis fungoides in advanced stages becomes a therapeutic challenge. During the course of the disease, the tumor may become treatment resistant. We report the use of pegylated liposomal encapsulated doxorubicin in a CD30-positive patient, who had become resistant to skin targeted PUVA treatment (psoralen plus UVA irradiation) and methotrexate. We achieved an objective global response lasting for seven months. Later on, the patient had a relapse and was no longer responding to doxorubicin, even with a dose escalation. A re-biopsy demonstrated the continuous expression of CD30, allowing a shift to CD-targeted treatment with brentuximab vedotin, a monoclonal antibody conjugate with monomethyl auristatin E. His objective global response lasted for six months, before he eventually deceased. CD30-targeted treatment is an option for mycosis fungoides with CD30 transformation.

Introduction

Mycosis fungoides (MF) is the most frequent disease in the spectrum of malignant cutaneous T-cell lymphomas (CTCL). Initially, it presents with macules that may resemble eczema or psoriasis, the course is indolent. Later on, plaques, palpable lymph nodes and tumors develop, which may undergo ulcerations and larger areas of the body surface, become involved. Some patients develop a secondary erythroderma (1).

Treatment of MF should be stage-adapted and overtreatment needs to be avoided. For instance, poly-chemotherapy provides excellent response rates but does not improve survival. Toxicities impair the quality of life and relapses are unavoidable. Therefore, the development of new treatment options is warranted (2).

Case report

In autumn 2015, a 79-year-old male patient presented with a confirmed diagnosis of MF with mycosis follicularis and CD-30 positive transformation (pT3cN0cM0B0 (stage IIB), that had been worsened during systemic methotrexate therapy (25 mg/week), psoralen plus UVA irradiation (PUVA), and topical potent corticosteroids.

He presented with large erythematous infiltrated nodules and tumors, partly ulcerated on the trunk, head and proximal extremities. Imaging investigations with computerized tomography (neck and trunk) and lymph node sonography were unremarkable. Laboratory investigations demonstrated a mild anemia with 4.20 erythrocytes/L (normal range 4.6-6.2 Tpt/L) and hemoglobin of 8.50 mmol/L (8.6-12.1 mmol/L). There was a
lymphopenia of 13.0% (20-45%), soluble interleukin-2 receptor was markedly increased with 898 U/mL (223-710 U/mL). Lactate dehydrogenase was 5.12 μkat/L (2.25-3.75 μkat/L), C-reactive protein was slightly increased with 9.2 mg/L (< 5 mg/L). In the peripheral blood, no Sezary cells were detected.

After cardiologic investigations, performed in order to exclude contraindications (electrocardiogram, echocardiography), an intravenous therapy with pegylated liposomal encapsulated doxorubicin (Caelyx®; 20 mg/m² body surface) was initiated and repeated every two weeks for a total of six cycles. Tumors on the head and face were targeted by electron bean irradiation. Topical treatment was realized with betamethasone ointment. Treatment was well tolerated. A minor oral gingivitis was treated with sage tea. Later on, an oral candidiasis developed, that was treated by oral suspension of amphotericin B.

The intractable pruritus disappeared almost completely, lesions became flat and hyperpigmented. We achieved an almost complete response. Topical corticosteroid application was continued.

For maintenance therapy, subcutaneous interferon alpha (Roferon A®, 3 x 3 mio U/week) was initiated in May 2016. Due to partial relapse, the interferon dosage was increased to 3 x 6 mil U/week in July and PUVA treatment was performed.

Intravenous liposomal encapsulated was reintiated in September 2016 due to further progress of his disease, pT3cN1cM0 (stage IIB). The dosage was escalated after two infusions from 20 mg/m² to 40 mg/m². After five cycles, however, the disease progress was not stopped. New tumors developed and the pruritus became distressing. We performed another skin biopsy to investigate the dynamics of the disease. We could confirm the continuous expression of CD-30 by tumor cells, allowing a targeted therapy approach.

In collaboration with the hemato-oncology department, brentuximab vedotin (Adcetris®) 1.8 mg/kg every three weeks was started using a central venous catheter. During the treatment, he developed temporarily febrile temperatures and fatigue. In between the first and second scheduled brentuximab vedotin application, he incurred a catheter sepsis (Staphylococcus aureus) that was treated in the intensive care unit with systemic antibiotics (fluocloxacilline and cephalaxine, later piperacilline/tazobactam, and eventually levofloxacin). After complete remission and exclusion of secondary cardiac involvement, antineoplastic therapy was continued. After the fourth infusion, he developed sepsis again and was therefore treated in the intensive care unit. In May 2017, he received the 5th infusion. MF lesions became flat and hyperpigmented, pruritus was improved. Palmoplantar erythro-dysesthesia, however, worsened during the course. Adverse effects of pegylated liposomal doxorubicine and brentuximab vedotin are listed according to the Common Terminology of Criteria for Adverse Events v4.0 in Table 1 (3).

Deplorably, four weeks later he deceased.

**Table 1.** Adverse events observed during treatment with pegylated liposomal doxorubicin (PEG-DOXO) and brentuximab vedotin (BV) according to the Common Terminology of Criteria for Adverse Events v4.0 (3)

<table>
<thead>
<tr>
<th>Gender</th>
<th>PEG-DOXO (20 mg/m²)</th>
<th>BV (1.8 mg/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Grade 1</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>-</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Malaise</td>
<td>-</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Chills</td>
<td>-</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>Grade 1</td>
<td>-</td>
</tr>
<tr>
<td>Palmo-plantar dysesthesia</td>
<td>-</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Peridontal disease</td>
<td>Grade 1</td>
<td>-</td>
</tr>
<tr>
<td>Sepsis</td>
<td>-</td>
<td>Grade 4</td>
</tr>
</tbody>
</table>

**Discussion**

MF is a malignant disease that is not curable yet. In early stages (IA and IB), patients have a normal life-expectancy. Our patient suffered from MF stage IIB. Established treatments for stage IIB MF include PUVA therapy, which can be combined with either interferon-alpha, bexarotene or radiotherapy for single tumors. Second-line treatments include methotrexate, gemcitabine, doxorubicin, and brentuximab vedotin (1, 2).

Doxorubicin is a DNA intercalating drug available in different pharmaceutical preparations with a variable safety profile. In contrast to classical doxorubicin, pegylated liposomal-encapsulated doxorubicin has lesser cardiotoxicity, concentrates higher in the skin (where MF is localized) and needs smaller dosages. It has been shown that pegylated liposomal encapsulated doxorubicin restored the altered galectin expression associated with loss of growth control. The preferred dosage for MF is 20 mg/m² every two weeks (4-6).

After complete or nearly complete remission, a maintenance therapy with PUVA, bexarotene or interferon-alpha is possible (2, 7). In the present case, interferon-alpha was not effective, leading to...
disease progression. Methotrexate and PUVA were not chosen since both failed before. The objective global response after the initiation of pegylated liposomal encapsulated doxorubicin lasted for seven months. Adverse events were tolerable (Table 1). Due to a relapse of the disease and loss of response to doxorubicin, alternatives had to be found.

In collaboration with the hemato-oncologists, brentuximab vedotin therapy was initiated. Brentuximab vedotin is a CD30-targeted monoclonal antibody conjugated to the microtubule-disrupting agent, monomethyl auristatin E, used in non-Hodgkin lymphomas. Monomethyl auristatin E is released to CD30-positive tumor cells, where it can block the spindle apparatus (8). Pro-apoptotic effects of the monoclonal antibody have also been discussed (9). The most common adverse effects are fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy (10).

In a phase-3 trial, 128 analyzed patients with either MF or primary cutaneous anaplastic T-cell lymphoma were treated either with brentuximab vedotin, or methotrexate or bexaroten. At a median follow-up of 22.9 months, the proportion of patients achieving an objective global response lasting at least four months was 56.3% with brentuximab vedotin versus 12.5% with one of the other compounds. Grade 3-4 adverse effects were recorded in 41% of the brentuximab vedotin group and in 47% of controls (11).

In our hands, objective global response lasted for six months. Adverse effects were infections (sepsis) and pronounced palmo-plantar dysesthesia. The increased risk of infection cannot solely be ascribed to brentuximab vedotin, disease progression as well. Targeted tumor therapy has become an alternative treatment in unresponsive MF cases.

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**Conflicts of interest:** none declared.