

Complete remission of primary cutaneous anaplastic large cell lymphoma after a short course of brentuximab vedotin

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Abstract. Primary cutaneous anaplastic large cell lymphoma (PCALCL) is a rare CD30⁺ lymphoproliferative disorder characterized by the development of lesions ranging from papules to large tumors. Most cases present as localized disease, however multifocal and generalized involvement of the skin can occur. Several treatments have been proposed for PCALCL; however a highly effective standard approach to multifocal disease has not yet been elucidated. The disease expression of CD30 antigen in at least 75% of the tumor makes it an optimal target for immunotherapy. The current study presents a case of a 62-year-old male referred to the University of Padua Dermatology Clinic complaining about nodular and ulcerated lesions involving the frontal area and scalp that were 8 cm in diameter. Doses of 180 mg brentuximab vedotin (BV), which is an antibody drug conjugate binding CD30 antigen, were administered every 21 days. A 75% decrease in dimensions after the first infusion and a complete remission after the second was observed. Disease response appeared to be dose-related and adverse reactions, in particular peripheral neuropathy, may be an effect of cumulative toxicity, meaning that treatment cycle reduction should be considered. Based on the present results, A high dose, short course of BV is recommended as a cost-effective approach for PCALCL. However, further studies are required to assess the efficacy and other potential advantages of this therapeutic regimen.

Introduction

Primary cutaneous CD30⁺ lymphoproliferative disorders (LPDs) are rare diseases but represent the second most frequent form of cutaneous T-cell lymphoma after mycosis fungoides (1,2). According to the 2018 update of the WHO-EORTC classification,

CD30⁺ T-cell LPDs range from lymphomatoid papulosis (LYP) to primary cutaneous anaplastic large-cell lymphoma (PCALCL) and constitute a spectrum of disorders expressing CD30 antigen in tumor cells (1,3,4). The two conditions feature different presentation and clinical course: LYP is characterized by papulonodular lesions undergoing spontaneous regression over a chronic course of years to decades, while PCALCL manifests with solitary or grouped, rapidly growing and ulcerating tumors or plaques. PCALCL typically affects older males and in 20% of cases presents multifocal skin involvement. In 30% of cases, PCALCL tends to spontaneous regression, yet to a lesser extent and duration than LYP (1). Diagnosis is based on histopathology and immunohistochemistry revealing CD30⁺ large pleomorphic or anaplastic T-cells; in PCALCL at least 75% of tumor cells are CD30⁺ (1,3). Extra-cutaneous disease spreading should be ruled out with staging procedures including whole body PET-CT scan and, in the case of multifocal tumors, extracutaneous disease and abnormal laboratory exams, bone marrow examination (1). Management of PCALCL should be tailored to each case taking into account the severity of cutaneous involvement and the indolent nature of the disease, with 5-year survival rates between 76-96% (1). The disease has an intrinsic tendency to skin relapse in ~39% of patients, associated to a limited risk of systemic spreading in only 13% of cases (2). In cases of localized disease, a wait-and-see strategy can be appropriate as spontaneous complete remission occurs in up to 22% of cases after a median period of 2 months (range 1-6 months) (1,2). Surgical excision or local radiation can be additionally considered based on tumor burden (2). The approach to multifocal or disseminate disease should consider that aggressiveness of therapy does not influence the frequency of relapse and that consequently the aim of treatment cannot be sustained remission. Alternatives in disseminate or progressive forms include single cytotoxic drugs, such as methotrexate, or polychemotherapy regimens based on anthracyclines, such as CHOP (3). Brentuximab vedotin (BV) has recently shown promising results in the treatment of PCALCL even if the optimal dosing is currently not defined.

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Case presentation

A 62-year-old Caucasian man was referred to our Dermatology Department complaining the abrupt appearance and quick advancement of cutaneous nodules, associated with a sensation

of skin pain and tenderness. The patient reported the onset of a single lesion in the right frontal region, progressively increasing in size since June 2019, followed by the appearance of other nodules in the scalp and finally by the rapid development of another nodular left frontal lesion in August 2019. The patient had a personal history of arterial hypertension, gastroduodenal ulcer and bilateral ischemic optic neuropathy in therapy with atenolol, perindopril, indapamide, amlodipine, acetylsalicylic acid and pantoprazole. Clinical examination revealed diffuse nodules on the scalp and on the frontal area, where the two major lesions, 4.5 cm diameter in the right frontal region (Fig. 1A) and 8 cm in the left, were observed. The nodular lesions were elevated ~3 cm from the surrounding skin, firm to touch and presented an ulcerated erythematous surface. The characteristics of lesions and the history of rapid growth were highly suggestive for a cutaneous localization of lymphoproliferative disease.

Multiple biopsy specimens were obtained in September and October, setting a differential diagnosis between LYP and PCALCL. A CT-scan ruled out extra-cutaneous localizations of disease and peripheral blood cytometry showed no abnormal immunophenotypes. Finally, a bone marrow specimen was obtained, and the results proved normal bone cellularity with no signs of cellular atypia and a maintained leuco-erythroblastic ratio.

As soon as the diagnosis was confirmed by histology, we started therapy with methotrexate 7.5 mg sc weekly and prednisone 25 mg po daily. At the follow-up visit, scheduled after one month, we found a size increase in the lesions and we raised the dose of methotrexate up to 15 mg weekly and considered alternative treatments. Because of the clinical extent and aggressive behavior of the disease we decided to start therapy with BV at the dosing of 180 mg (1.8 mg/kg) every three weeks. Clinical assessment at three weeks from the first infusion of BV showed an important decrease in volume of lesions, with the prominent left frontal reduced to 3.5 cm and the right one to less than 1 cm in diameter. Two weeks after the second infusion, we appreciated a complete remission of all skin lesions with only mild hyperpigmented and fibrotic results (Fig. 1B).

The patient is scheduled for 16 infusions of brentuximab 180 mg every three weeks, four of which have been already administered. The disease is in complete remission and the patient complained no adverse events following treatment. Monthly monitoring of laboratory tests before and during treatment showed no abnormal values.

Discussion

Currently, there is no standard therapeutic approach for cases of multifocal PCALCL. Combination chemotherapy has been frequently administered for multifocal primary cutaneous disease, even though no specific regimen has been reported as superior and doxorubicin-based combinations, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), are more frequently used. On the basis of a review by Shehan *et al* relapses seem to occur more frequently in patients receiving traditional chemotherapy and this result doesn't correlate with a more aggressive treatment of extensive disease (3). Moreover, the Dutch Cutaneous Lymphoma Group



Figure 1. Primary cutaneous anaplastic large cell lymphoma. (A) Nodular lesions on the right frontal region at baseline and (B) at clinical reassessment two weeks after the second infusion of brentuximab vedotin.

found that all patients treated with CHOP regimen developed one or more relapses in the skin and authors suggested not to use traditional chemotherapy for multifocal ALCL involving the skin (5). Radiotherapy or low-dose methotrexate, that was initially administered to our patient, have also been proposed as first-line treatment for multifocal or relapsing PCALCL limited to skin (5,6). Moreover, systemic retinoids including bexarotene, interferon alpha-2a and thalidomide have been effective treatments for multifocal PCALCL (1). Etoposide monotherapy and autologous bone-marrow transplantation have also been proposed for relapsed multifocal disease (3).

Finally, BV is an antibody-drug conjugate (ADC) that combines a chimeric anti-CD30 antibody to the anti-microtubule agent monomethyl auristatin E (MMAE) (7,8). Upon binding to CD30 receptor, the ADC is internalized by endocytosis and undergoes consequent lysosomal degradation allowing MMAE to bind microtubules and cause cell cycle arrest and apoptosis (7). CD30 is a cell surface leukocyte antigen constituted by a type I transmembrane glycoprotein and an extracellular domain homologous to tumor necrosis factor and nerve growth factor receptor family members. CD30 is normally expressed in activated T, B, and natural killer lymphocytes. Certain LPDs (including Hodgkin lymphoma, ALCL, CTCL, a fraction of diffuse large B-cell lymphomas and of follicular lymphomas) and Kaposi sarcoma express the CD30 antigen as well (2,9). The function of CD30 has not been defined yet, but it seems implicated in both cell death and proliferation (9). Targeted delivery of MMAE to

CD30 expressing tumor cells makes BV a well-suited target for immunotherapy. Based on our observation of significant disease response after the first BV infusion and complete remission after the second one, we suggest that high-dose short course therapy with BV could be an appropriate approach for PCALCL. While therapeutic management of Hodgkin lymphoma (HL) with BV is better established and more clinical data are available, PCALCL treatment protocol is not yet well defined. BV is approved by the FDA for both HL and ALCL at an intravenous dose of 1.8 mg/kg every 3 weeks (7). While treatment is usually administered for a maximum of 16 cycles or until either disease progression or unacceptable toxicity occur, multiple studies have been conducted in recent years with different dosing regimens of BV (7). Fanale *et al* in a phase I study with CD30⁺ LPDs administered a 0.4-1.4 mg/Kg/dose weekly for 3 weeks every 28 days obtaining an overall response rate (ORR) of 59% and a complete response (CR) of 34% (10). A phase II study of BV in PCALCL enrolled 11 patients receiving six doses each of 0.4-1.2 mg/kg, achieving an ORR of 82% and a CR in 55% of cases (9). Though limited, these results support the hypothesis that clinical response to BV in PCALCL could be dose-related and suggest use of maximal dosing equivalent to 1.8 mg/kg. Moreover, the fast response observed in our case report could be explained by the high percentage of CD30⁺ cells present in PCALCL on which the drug exerts a targeted mechanism of action. PCALCL expresses CD30 antigen in at least 75% of tumor mass, thus implicating that after each cycle of BV ~75% of cells die as a result of direct killing. In addition, such a rapid dimensional decrease could be the result of an indirect action of BV. In fact, MMAE produce a well-known toxic effect by diffusing into surrounding stroma, destroying not only cells internalizing the ADC but also proximal tumor cells (7). Furthermore, our patient experienced a quick reduction in lesion size after the first dose, which is consistent with the pharmacokinetics of MMAE gaining maximum concentration approximately 1-3 days post infusion (7).

High dose protocols over a short course may be associated with a beneficial safety profile. Therapy with BV has been related to toxicities mostly of grade 1 or 2. The most common adverse reactions, observed in >20% of cases, have been peripheral sensory neuropathy, fatigue, diarrhea, neutropenia, vomiting, pyrexia, anemia, upper respiratory tract infections, fever, thrombocytopenia (7,11). However, serious adverse reactions such as peripheral motor neuropathy, septic shock, supraventricular arrhythmia, progressive multifocal leukoencephalopathy and one case of Steven-Johnson syndrome were reported in phase II trials (7). Peripheral neuropathy is the most common side effect, experienced by 55% of patients, responsible for treatment discontinuation in 12% of cases and for dose-reduction in 10% (7). Moreover, this side effect seems to be more common when the drug is administered weekly rather than every three weeks. Younes *et al* reported 22% of patients experiencing peripheral neuropathy with 1.8 mg/kg every 3 weeks of BV compared to 66% of cases described by Fanale *et al* with a weekly dose of 0.4-1.4 mg/kg (10,12). Although usually reversible, peripheral neuropathy is typically an effect of cumulative toxicity, thus encouraging reduction in number of cycles and frequency of administration (7).

In the end, considering an estimate cost of ~200.000 euros for 16 cycles of BV in a patient of 80 kg, a short cycle may considerably improve cost-effectiveness (13).

In conclusion, PCALCL has a generally indolent behavior even in disseminated presentations and shows frequent cutaneous relapses that maintain responsiveness to treatments. Well-designed clinical trials are needed to determine the efficacy of high dose short course therapy with BV and to assess whether there are other potential advantages over standard 16 cycle protocol.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EM, PM and AS prepared the manuscript. EM and PM performed the literature analysis search. AS, MA, SF and DM conceived and designed the current study. AS and MA drafted and critically revised the manuscript for important intellectual content. AS prepared the figures. MA gave final approval of the version to be published. All authors read and approved the final manuscript. MA and AS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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