Treatment of leptomeningeal disease in blastic plasmacytoid dendritic cell neoplasm following tagraxofusp-erzs induction

Treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) has significantly improved following the introduction of tagraxofusp-erzs (SL-401), a cytotoxic immunotoxin targeting CD123/IL-3 receptor α.[1] However, management of this rare hematologic malignancy remains demanding considering its aggressiveness with an often dismal outcome. Particularly leptomeningeal manifestation of BPDCN poses significant challenges. Here, we report diagnostics and successful hematopoietic stem cell transplantation of a first BPDCN patient initially treated with tagraxofusp-erzs and subsequently developing leptomeningeal disease. The significance of early disease detection in cerebrospinal fluid and the importance of central nervous system (CNS) directed chemotherapy are highlighted.

A 52-year-old previously healthy house painter was referred to our department for evaluation of an allogeneic hematopoietic stem cell transplantation (HSCT) in April 2021. Approximately 5 months prior to referral, the patient presented with multiple circumscribed brownish, partly violaceous plaques up to 4 cm on his trunk and head (Figure 1A). Besides, the patient had enlarged cervical, axillary, and inguinal lymph nodes. A full body computerized tomography (CT) scan revealed additional lymphadenopathy in the mediastinum and portocaval region. Infectious diseases were excluded serologically and by polymerase chain reaction. Cytology and immunophenotyping (IPT) of peripheral blood and bone marrow samples did not show any signs of lymphoma, leukemia, or other hematologic diseases. Surgical biopsies of several skin lesions and an inguinal lymph node confirmed the diagnosis of CD4+CD56+CD123+ BPDCN.

The patient was treated with three cycles of the anti-CD123 antibody tagraxofusp-erzs. Apart from an elevation of liver enzymes during the first treatment cycle, tagraxofusp-erzs was well tolerated. The patient showed complete remission (CR) of the skin lesions and lymphadenopathy. A brain magnetic resonance imaging (MRI) in April 2021 did not reveal any pathological findings. The patient's brother was identified as an HLA-identical stem cell donor for consolidative allogeneic HSCT.

A week before planned HSCT the patient was admitted to another hospital with acute onset dysarthria. Neurological examination showed slightly atactic upper extremities. Cerebral ischemia was excluded by CT including angiography. However, there were multiple cortical contrast medium enhancements on an MRI-scan which were indicative of leptomeningeal disease. A lumbar puncture (LP) revealed a cell count of >7x10^9/L. Cerebrospinal fluid (CSF) was examined cytologically (Figure 1B) which demonstrated large blastic cells with lobulated nuclei. IPT showed positivity for CD4 and CD56, thus confirming the suspected diagnosis of leptomeningeal BPDCN recurrence (Figure 1C). At that time, additional extracerebral manifestations were excluded by positron emission tomography (PET)-CT scanning.

The patient was treated with high-dose methotrexate (HD-MTX; 4 g/m^2) and ifosfamide (2 g/m^2) as well as bi-weekly intrathecal therapy comprising methotrexate, cytarabine, and dexamethasone. During hematopoietic regeneration autologous peripheral blood stem cells were harvested. After two cycles of systemic treatment and four courses of intrathecal chemotherapy the patient showed full neurologic recovery and BPDCN cells were cleared from the CSF. Following consolidation with high-dose chemotherapy (carmustin/ BCNU 400 mg/m^2 and thiotepa 20 mg/kg) and subsequent autologous HSCT the patient recovered without major complications (Figure 2).

Over the next 2 months the patient did not show any clinical signs of BPDCN recurrence and a PET-CT scan as well as further CSF analysis confirmed a CR. Thus, the patient was admitted for consolidative allogeneic HSCT after conditioning with fludarabine (150 mg/m^2), busulfan (6.4 mg/kg), and post-transplantation cyclophosphamide (100 mg/kg).[2] Apart from a period of short bacteremia, he recovered without further complications. Immunosuppressives were tapered over the next 100 days without major graft-*versus*-host disease (GvHD). Ten months after CNS recurrence of BPDCN the patient is in CR and excellent clinical condition (Figure 2).

BPDCN is a rare disease accounting for less than 0.5% of all hematological malignancies.[3,4] Skin involvement is the most common feature, present in more than 85% of cases.[5] Recently, Pemmaraju *et al.* retrospectively analyzed 103 patients, of which only 29 had received LP (57% performed routinely at diagnosis) over the course of their disease.[6] Of these patients, 13 had frontline CNS disease and ten developed overt CNS disease over the course of time, respectively. In another recently published Italian cohort of 68 patients, four patients presented with frontline CNS disease and two developed CNS recurrence (70% routine CSF exams at diagnosis).[7] These studies indicate the importance of CNS involvement in BPDCN, but also show, that routine CNS testing and prophylactic intrathecal treatment have

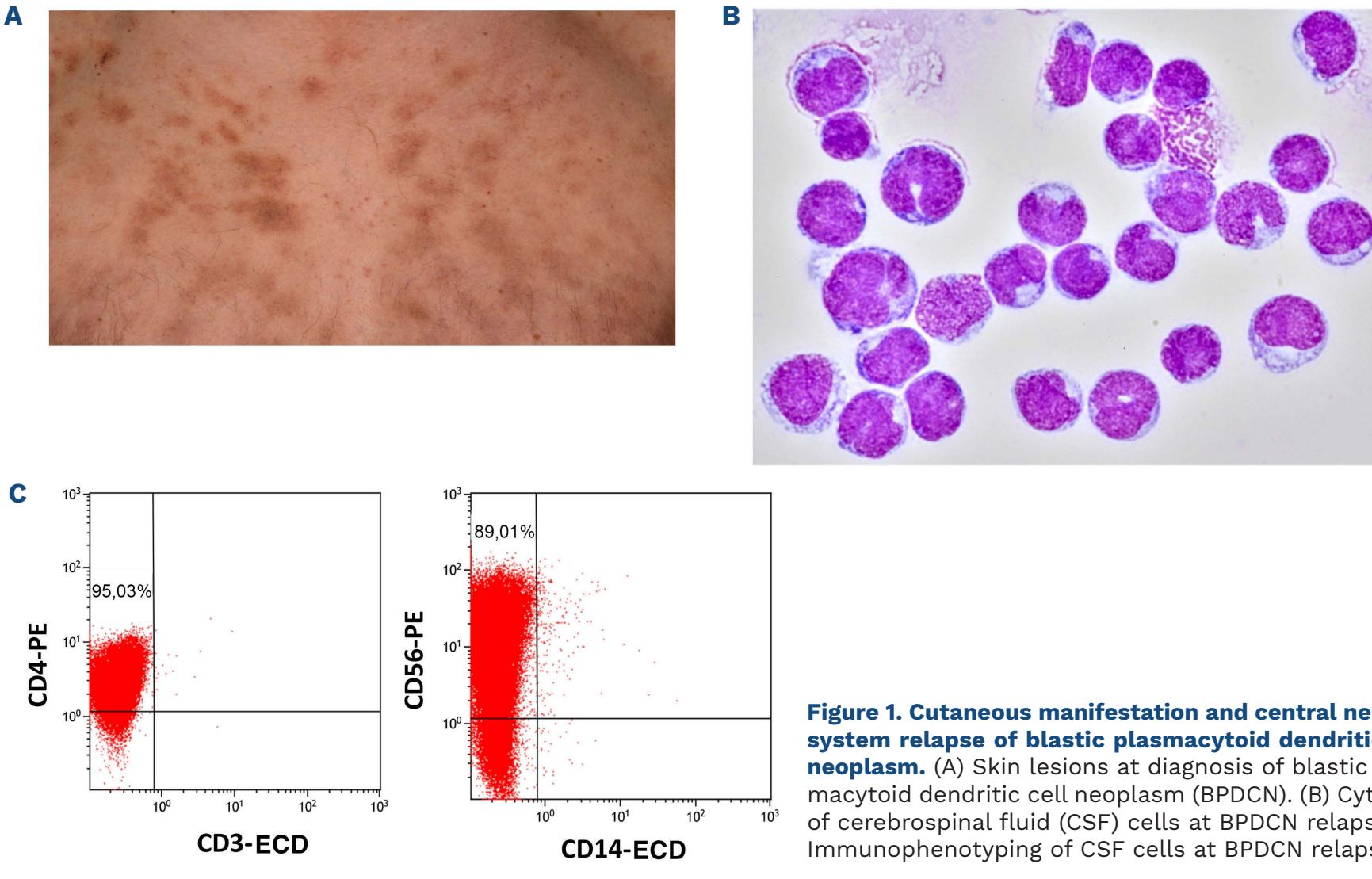

Figure 1. Cutaneous manifestation and central nervous system relapse of blastic plasmacytoid dendritic cell neoplasm. (A) Skin lesions at diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN). (B) Cytology of cerebrospinal fluid (CSF) cells at BPDCN relapse. (C) Immunophenotyping of CSF cells at BPDCN relapse.

not been implemented so far, despite clinical practice guidelines (NCCN 2022[8]) and some data suggesting a benefit of acute lymphoblastic (ALL)-like treatment protocols including intrathecal treatment.[9,10]

The anti-CD123 antibody-immunotoxin conjugate tagraxofusp-erzs (SL-401) received Food and Drug Administration and European Medicines Agency approval as upfront single agent after the results of a single arm phase I/II trial.[11] In this study, patients with known CNS involvement were excluded. CNS relapses were not detected throughout the study. Notably, routine LP had not been performed. Even more recently, an analysis of intensive and CNS active upfront chemotherapy (HCVAD) *versus* SL-401 did not reveal any CNS relapses in the targeted therapy group.[12]

To the best of our knowledge, our case is the first fully published CNS relapse after successful induction treatment with tagraxofusp-erzs. Our case adds to recently published data on CNS involvement in BPDCN.[7,8,12] Furthermore, it conveys three important messages: first, LP is an essential initial diagnostic procedure in BPDCN, also in the context of therapy with tagraxofusp-erzs. Due to their distinct morphology and aberrant immunophenotype BPDCN cells can be easily detected (Figure 1B and C). This has been highlighted in several studies and has been incorporated in current expert-guidelines.[8] Since our patient had not received any CSF cytology prior to induction therapy, unrecognized CNS involvement at diagnosis cannot be ruled out. Considering the clinical significance and the treatability, sensitive detection of CD4+CD56+CD123+ CSF cells, e.g., by next-generation flow cytometry,[10] is strongly recommended in each BPDCN patient at diagnosis.[8]

Second, although the rates of CNS manifestations are currently unknown under CD123-targeted therapy with tagraxofusp-erzs, they obviously do occur. One explanation is the missing capability of the antibody tagraxofusp-erzs to cross the blood-brain barrier. Considering historical data utilizing CNS active ALL protocols for BPDCN treatment, intrathecal prophylaxis and/or HD-MTX might be options and should be evaluated in any further clinical trial. Indeed, three cases have been reported as abstract, although these patients were treated without hematopoietic stem cell transplantation.[13] Our case underlines the cytotoxic effectiveness of the chosen treatment regimen against BPDCN cells and points to the importance of allogeneic HSCT.

Finally, in case of CNS disease treatment in analogy to CNS lymphomas incorporating HD-MTX and other CNS- penetrating drugs in combination with intrathecal chemotherapy as well as high-dose chemotherapy including autologous HSCT offers a feasible option which led to CR in our patient.[13,15] Nevertheless, allogeneic HSCT at the moment remains the consolidation treatment of choice for eligible patients.[15,16] As CR prior to allogeneic HSCT is an important prognostic factor,[17] we decided to first treat CNS relapse intensively including high-dose chemotherapy with

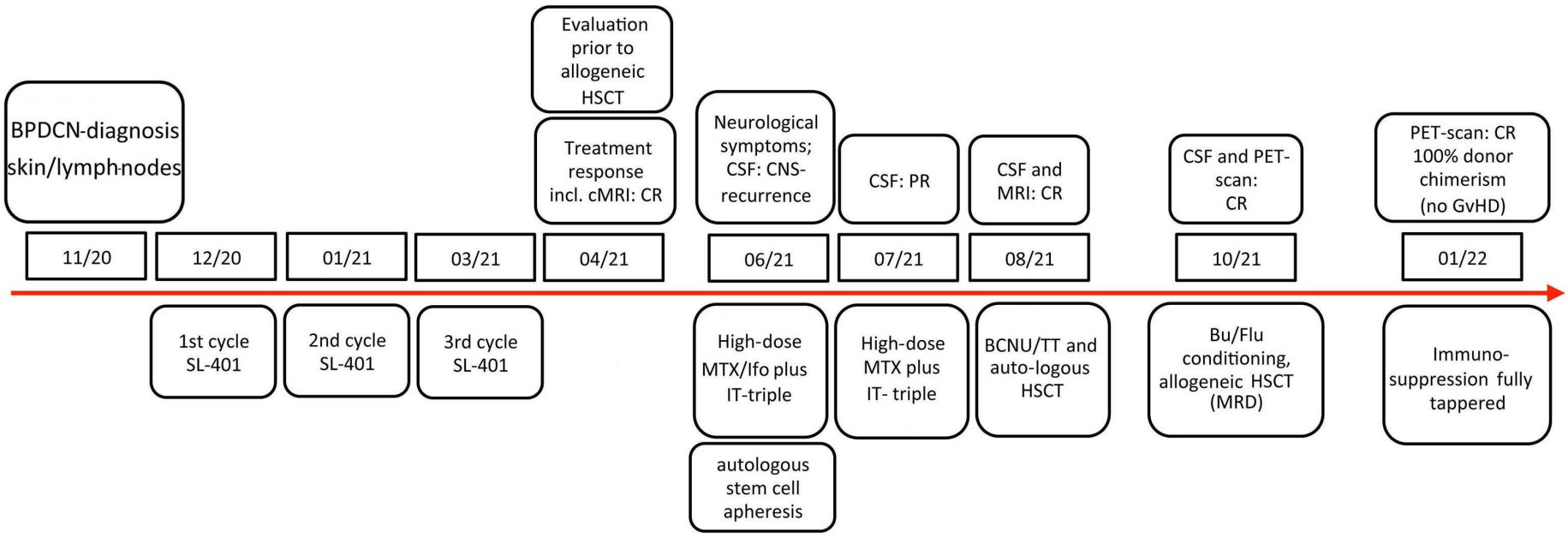

Figure 2. Blastic plasmacytoid dendritic cell neoplasm disease course and treatment time-line. BPCDCN: blastic plasmacytoid dendritic cell neoplasm; HSCT: hematopoietic stem cell transplantation; MTX: methotrexate; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; CNS: central nervous system; PR: partial remission; CR: complete remission; PET: Positron emission tomography; GvHD: graft-*versus*-host disease: IT-triple: triple intrathecal treatment.

autologous HSCT and conduct allogeneic HSCT following a slightly modified conditioning regime previously reported in primary CNS lymphoma by our group.[2] In order to achieve the maximum therapeutic effect, our treatment approach encompassed a broad spectrum of CNS effective drugs, including MTX, thiotepa, BCNU, and busulfan, as previously established within CNS protocols.[14,15] Ifosfamide was administered to facilitate early blood stem-cell collection.[15] Considering overall cumulative toxicity, we decided against myeloablative conditioning prior to allogeneic HSCT.

In summary, CNS involvement should be suspected right from the start with any BPDCN diagnosis and CNS manifestation can be treated by protocols analogous to CNS lymphoma. Realizing the frequency of occult CNS disease, early addition of prophylactic treatment with e.g., MTX should be considered as part of the initial therapy with tagraxofusp-erzs in routine and within future clinical studies.

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Disclosures

No conflicts of interest to disclose.

Contributions

DV, TG, and RS guided diagnosis and treatment of the patient and wrote the manuscript. DV, VN, TM, TG, and RS collected the data. All authors discussed the data and manuscript.

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