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CASE REPORT

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Complete hematologic response in a patient with multiple pretreated angioimmunoblastic T-cell lymphoma after belinostat therapy followed by allogeneic stem cell transplantation: A case report

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Key Clinical Message

Belinostat therapy followed by hematopoietic stem cell transplantation is a promising salvage strategy for heavily pretreated patients with peripheral T-cell lymphoma.

Abstract

Effective treatments for peripheral T-cell lymphoma in the relapsed and refractory (r/r) setting are limited. However, with the development and approval of innovative therapies, effective therapeutic options are becoming available for this patient population. This case report describes the treatment course of a patient with multiple r/r nodal follicular T-helper cell lymphoma of angioimmunoblastic type. Treatment with the histone deacetylase inhibitor belinostat as bridging, enabled allogeneic stem cell transplantation and resulted in a durable complete hematologic response for at least 21 months post-transplantation.

KEYWORDS

allogenic stem cell transplantation, belinostat, HDAC inhibitor, nTFHL-AI, PTCL

1 | INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) represent a heterogenous group of highly aggressive lymphoid malignancies, which are derived from mature T-cells or natural killer (NK)/T-cells and constitute approximately 15%–20% of all non-Hodgkin's lymphomas (NHL) in Western populations.[1] Typically diagnosed at advanced stage, PTCLs exhibit poor treatment outcomes, with a 5-year survival rate of 30%–40%.[2] According to the World Health Organization (WHO) classification, mature T-cell and NK-cell neoplasms are classified based on a combination of morphologic, immunophenotypic, genetic, and clinical features.[3] The most prevalent PTCL subtypes include nodal follicular T helper cell lymphomas (nTFHL) whose prototype is nTFHL of the angioimmunoblastic-type (nTFHL-AI), PTCL not otherwise specified (PTCL-NOS), and anaplastic large cell lymphoma (ALCL).[3]

Due to the rarity of PTCLs, only few randomized, prospective, and controlled studies have been conducted and their outcomes could be valuable in guiding treatment. Most therapeutic approaches for PTCLs have been derived from treatments developed for aggressive B-cell NHLs.[4] Anthracycline-containing regimens like cyclophosphamide,

doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens have historically been the standard, although response rates obtained so far are unsatisfactory. Approximately 75% of patients fail to respond or experience relapse, often within the first one to 2 years post-treatment.[5] Consolidating stem cell transplantation (SCT) is part of treatment protocols and represents a potentially curative treatment approach. However, about two thirds of PTCL patients are not eligible for hematopoietic stem cell transplantation (HSCT) due to the progression of the disease or because of their age, comorbidities, or poor performance status.[6] Patients with relapsed or refractory (r/r) PTCL face dismal prognoses, with median overall survival (OS) of 5.5 months and progression-free survival (PFS) of 3.1 months.[7]

Recent advances in the molecular subtyping of lymphomas and understanding of their underlying biology have led to the development of new targeted treatment options for NHL. In recent years, the US Food and Drug Administration (FDA) has approved several new targeted agents for the treatment of r/r PTCLs: the histone deacetylase inhibitors (HDACis) belinostat, romidepsin and chidamide, as well as the anti-folate agent pralatrexate and the CD30 drug-antibody conjugate brentuximab vedotin (BV).[8] The 2024 updated National Comprehensive Cancer Network (NCCN) guidelines for T-cell lymphoma are also mentioning these new treatment options, while supporting the search for evidence-based treatment strategies.[9] Belinostat—a hydroxamic acid-derived pan-HDAC inhibitor—received FDA approval in 2014 for the treatment of relapsed PTCL,[10] based on the outcomes of the BELIEF study, which demonstrated belinostat's ability to induce a durable overall response rate (ORR) of 25.8% (complete response [CR], 10.8%; partial response [PR], 15.0%) along with a highly favorable safety profile.[11] The median duration of response (DoR) reached 14 months, the median PFS 2 months and the median OS 8 months.[10,11] In patients with nTFHL-AI subtype, subgroup analysis revealed particularly high rates of ORR (45.5%) and CR (18.0%).[12] Importantly, belinostat monotherapy allowed a significant proportion of treated patients to undergo HSCT, which was associated with an increased OS.[11]

In this report, we present the case of a heavily pretreated patient with nTFHL-AI who underwent successful allogeneic SCT (allo-SCT) following belinostat therapy and achieved sustained complete hematologic response.

2 | CASE PRESENTATION

2.1 | Medical history

In October 2019, a 60-year-old male patient presented to our Department of Hematology and Oncology with complaints of lymphadenopathy. His medical history included appendicitis, tonsillectomy, surgery for hallux valgus, dyslipidemia, and spondylolisthesis. The patient also reported diffuse erythema in April 2018, with recurrence in August 2019 which was treated with bilastine twice daily. He also reported suffering from knee problems and occasional left sciatica from time to time. Since September 2019, the patient had a persistent dry cough and swollen lymph nodes, with mild sore throat and occasional abdominal pain. The patient did not present allergies or any intoxication with alcohol or tobacco. He exercised regularly and had a good performance status (ECOG 0). In his family, his mother had a stroke and a breast neoplasm.

2.2 | Diagnostic procedures

A clinical examination revealed multiple adenopathies, including bilateral cervical and supraclavicular, left axillary and left inguinal. No hepatosplenomegaly was detected per abdominal ultrasound examination. Initial blood tests including a flow cytometric analysis, revealed an atypical T-cell population (64% LyT CD3 lo/$CD5^+$/$CD2^+$/$CD7^+$/$CD4^+$/$CD10^+$/$TCRab^+$/$CD1a^-$/$CD25^-$/$CD16^-$/$CD56^-$/CD57 majority), possibly indicative of angioimmunoblastic T-cell lymphoma (nTFHL-AI)[13,14] or another follicular T-cell lymphoma with profound B-cell lymphopenia. A positron emission tomography-computed tomography (PET-CT) performed in October 2019 showed the following hypermetabolic foci: multiple adenopathies in the thoracic region (left and right axilla, left and right pulmonary hilus, mediastinum), as well as bilateral inguinal and discrete bilateral iliac adenopathies (Figure 1). A moderate diffuse bone marrow hypermetabolism was also observed. The histological examination performed after biopsies of the mediastinum confirmed the diagnosis of an ALK1-negativ, CD30-positive, PD1 and ICOS positive, Ki67 15%, $CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, $CD10^+$, $BCL6^+$, PAX5-, nTFHL-AI NHL, with monoclonal T-cell receptor gamma (TCR-γ) and TCR-beta (TCR-β) rearrangement. A bone marrow biopsy (BMB) revealed an infiltration by nTFHL-AI but no TCR-γ rearrangement. A normal male karyotype 46,XY [1] was established. The patient was considered as high risk in AITL score (age, CRP, β2).[15]

2.3 | Treatments and outcomes

Between October and December 2019, the patient was administered four cycles of BV in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) as first-line therapy. After two cycles of BV-CHP, a CR was confirmed by PET-CT (Figure 2). This allowed a BEAM

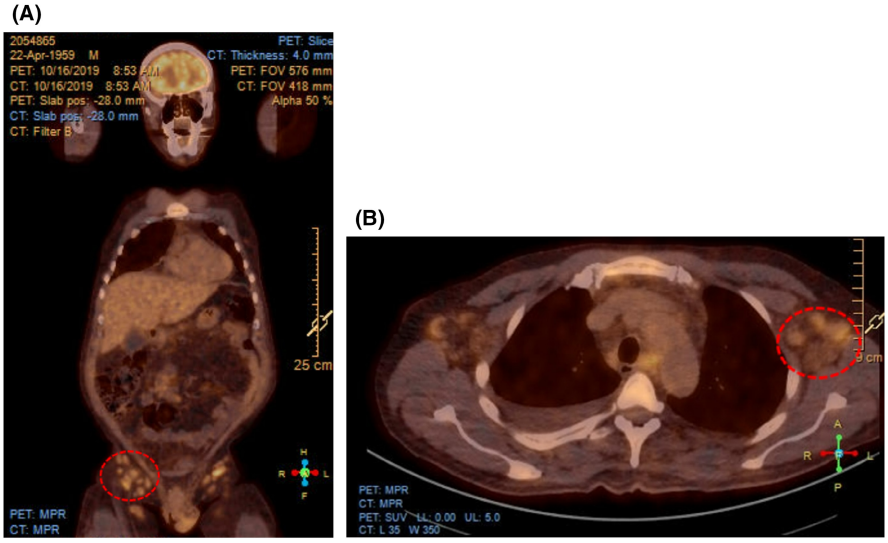

FIGURE 1 Initial PET-CT from October 2019 with multiple adenopathies: (A) bilaterally in the inguinal region, discrete adenopathies bilaterally in the iliac region, in the thoracic region, (B) left and right axilla, left and right pulmonary hilus, mediastinum). PET-CT, positron emission tomography computed tomography.

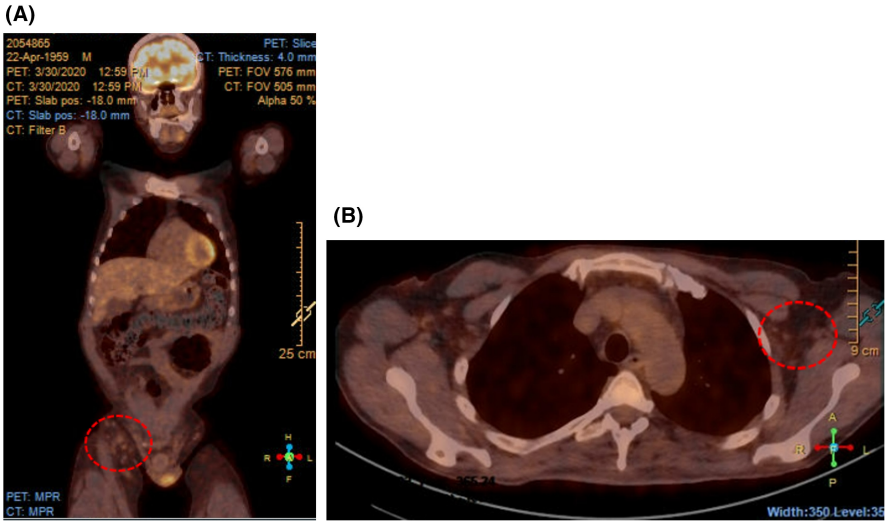

FIGURE 2 PET-CT performed after two cycles of B-BV therapy: (A) iliac region, (B) axillar region. B-BV, bendamustine plus brentuximab vedotin; PET-CT, positron emission tomography computed tomography.

(carmustine, etoposide, cytarabine, and melphalan)-conditioned autologous stem cell transplantation (auto-SCT) to be performed in January 2020. Side effects included skin erythema on discharge from the aplasia (lasting 10 days) and after 48 h of ceftazidime. Corticosteroids were required due to suspected engraftment syndrome. The initial results of the auto-SCT were promising; PET-CT showed an ongoing CR (Figure 3).

The patient received maintenance therapy with BV for 12 cycles until November 2020.

In February 2020, the patient developed pneumonia caused by cytomegalovirus (CMV) infection, that could successfully be treated with piperacillin/tazobactam, moxifloxacin, ganciclovir, followed by valaciclovir (orally, 450 mg, twice daily).

In May 2021, the patient underwent complete screening for skin lesions, skin histology revealed superficial perivascular and interstitial dermatitis consistent with hypersensitivity dermatitis. A PET-CT was negative, but a bone marrow biopsy showed a residual infiltration of T-cell lymphoma with secondary eosinophilia. A positive expression of PD1 and ICOS supported the suspicion of bone marrow localization of the nTFHL-AI. But no TCR-γ and TCR-β rearrangements were detected. So, close follow-up was recommended and therefore, no new treatment was initiated at this time.

Six months later, in November 2021, the patient reported persistent, intermittent new skin lesions. A PET-CT revealed the recurrence of several hypermetabolic thoracic, left inguinal and right iliac lymph nodes. A newly performed biopsy of the left inguinal lymph node confirmed the recurrence of the nTFHL-AI. Treatment with bendamustine-brentuximab vedotin (B-BV) was therefore initiated in December 2021. However, after three cycles of B-BV, the PET-CT in January 2022 showed a progression of the malignant disease.

Given the resistance of the disease, the decision was made to start an ifosfamide, carboplatin, etoposide (ICE)-based chemotherapy, followed by familial allogenic stem cell transplantation (allo-SCT). However, the ICE

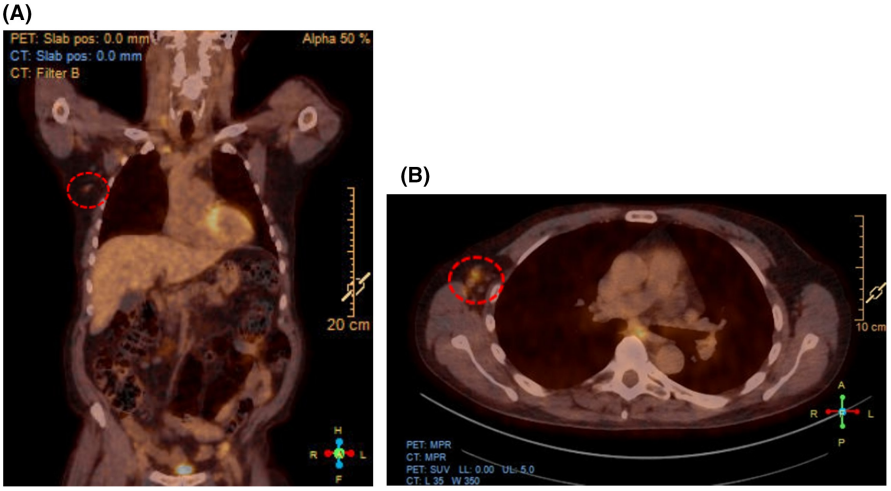

FIGURE 3 PET-CT after BV-CHP treatment and subsequent BEAM-conditioned autologous stem cell transplantation of the (A) thoracic region and the (B) iliac region. BEAM, carmustine, etoposide, cytarabine, and melphalan; BV-CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; PET-CT, positron emission tomography-computed tomography.

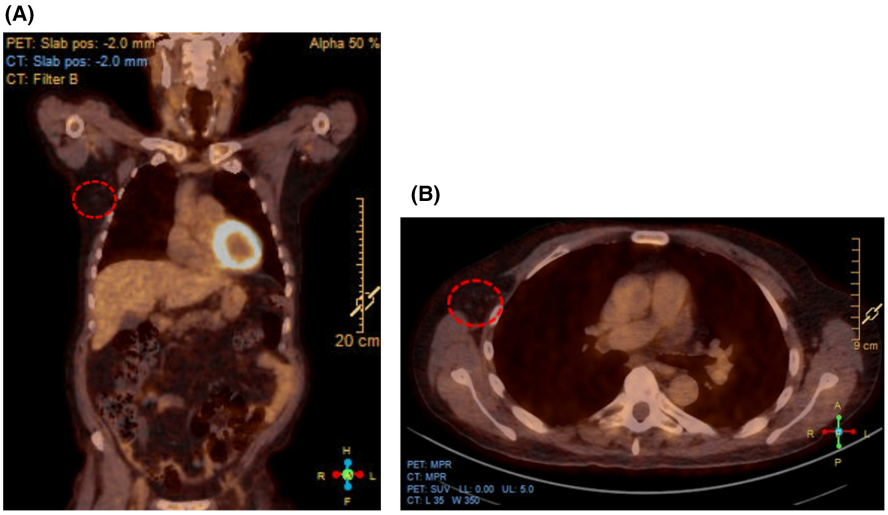

FIGURE 4 PET-CT performed after four cycles of belinostat therapy (1000 mg/m^2): (A) thoracic region, (B) axillar region. PET-CT, positron emission tomography computed tomography.

chemotherapy proved to be complicated as the patient developed severe thrombocytopenia with complete intolerance to platelet transfusions. In March 2022, however, complete remission was confirmed by a new PET-CT and the allo-SCT was planned shortly after the patient had profited from a weekend with his family.

In April 2022, shortly before the allo-SCT could be performed, the patient was admitted to the intensive care unit due to a severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2) pneumopathy and a *Klebsiella pneumoniae* superinfection, followed by a sepsis, an acute renal failure, a coagulopathy, and a thrombocytopenia (48.000/μL). The patient received an antibiotic therapy with piperacillin/ tazobactam, anidulafungin, linezolid, meropenem, as well as a transfusion of one unit of erythrocytes and required oxygenation. A week later, the patient was discharged from hospital with complete spontaneous resolution of the renal failure; however, the PCR tests continuously detected SARS-CoV2.

In May 2022, a PET-CT identified two suspicious paratracheal lymph nodes. Following discussions with transplant specialists, it was decided to carry out a fourth cycle of ICE because of the patient's persistent SARS-CoV2 positivity.

In July 2022, the patient finally tested negative for SARS-CoV2 for the first time, allowing for a new evaluation at the transplant center: A PET-CT revealed that the nTFHL-AI was in progression despite the fourth ICE cycle: hypermetabolic sub- and especially supra-diaphragmatic adenopathies associated with hypermetabolic splenomegaly and relatively homogeneous diffuse bone marrow hypermetabolism were detected. A clinical progression included erythema, paraneoplastic fever, disseminated intravascular coagulation, lactate dehydrogenase (LDH) elevation, capillary leak syndrome, cardiac decompensation, and signs of macrophage activation syndrome. The decision was therefore made to initiate treatment with the HDAC-inhibitor belinostat.

In the period from July to September 2022, a total of four cycles of belinostat treatment (1000 mg/m^2, intravenously [i.v.], Day 1–Day 5 of a 21-day cycle) were performed. Belinostat therapy resulted in a positive clinical response, which was confirmed by a PET-CT in

September 2022 showing a CR with a Deauville Score of 1 (DS1) (Figure 4). Considering the health improvement of the patient, a consolidating allo-SCT was finally realized.

The therapeutic approach of the consolidating allo-SCT included reduced-intensity conditioning (RIC) regimen comprising fludarabine (30 mg/m^2, i.v., Day 6 to Day 2), melphalan (100 mg/m^2, i.v., Day 2), and thymoglobulin (2.5 mg/kg/d, Day 2 and Day 1). A human leukocyte antigen (HLA)-related allo-SCT was performed mid-October 2022; peripheral stem cells (PSCs) from the patient's sister were obtained after stimulation with G-CSF and reinfused into the patient at 551×10^6 CD34+ or 6.3×10^6 CD34$^+$/kg. Anti-T-lymphocyte globulin (ATG), mycophenolate mofetil (MMF) and tacrolimus were used for immunosuppression and prevention of graft versus host disease (GvHD). As prophylaxis against potential CMV reactivation, the patient also received letermovir. A chemotherapy-induced diarrhea and nausea with vomiting (grade 1) were treated symptomatically. A hypokalemia/magnesemia was substituted intravenously. On Day 6, the patient experienced febrile neutropenia due to sepsis caused by an oxacillin-resistant *Staphylococcus epidermi*, which was treated with both antibiotics meropenem and vancomycin for 8 days. On the hematological level, the patient experienced chemotherapy-induced pancytopenia with grade 4 neutropenia (<500 neutrophils/μL), which persisted for 12 days and then normalized without G-CSF support. The patient also experienced Grade 3 anemia (min. 7.1 g/dL), and grade 4 thrombocytopenia (min. 5000/μL). In addition, he also had an acute renal failure (max. creatinine 2.12 mg/dL), presumably triggered by acute tubulonecrosis due to vancomycin toxicity but with recuperation of normal renal function after cessation of vancomycin treatment.

Mid-November 2022, after a 1-month stay in hospital, the patient was finally able to go home. The immunosuppression was discontinued in March 2023; both PET-CTs performed in April 2023 and October 2023 confirmed persistent complete hematological response. At his last follow-up appointment in May 2024, the patient was in good general condition; he declared going for a walk every day without any problems and has done several vacations. He enjoys a perfect quality of life, is gardening and having a normal social life.

3 | DISCUSSION

Unfortunately, only 30% of patients with r/r PTCL achieve response with current treatment options and long-term survival is relatively poor; in addition, approximately two-thirds of patients with r/r PTCL are not eligible for a HSCT.[5,6] It is therefore of great importance to identify successful treatment pathways for this difficult-to-treat patient group.

The patient in this case report had a CD30$^+$ nTFHL (formerly known as angioimmunoblastic T-cell lymphoma, AITL) which was refractory to multiple lines of treatment. Due to the CD30 positivity, the initial treatment involved the anti-CD30 antibody-drug conjugate BV in combination with a CHP regimen. CD30-expression is found in many PTCL subtypes; while systemic ALCL show uniformly a strong expression of CD30, 21% of nTFHL-AI were found to express CD30 by immunohistochemistry (score of ≥2).[16] The phase III ECHELON-2 trial demonstrated that BV-CHP significantly improved PFS and OS compared to standard CHOP therapy in untreated CD30-positive PTCL patients.[17] Notably, patients achieving a complete remission (CR) under BV-CHP followed by a consolidated SCT exhibited particularly favorable outcomes, with a median PFS follow-up of 55 months after BV-CHP without transplant and not reached following SCT.[18] Based on these positive results, BV-CHP was approved by the FDA in 2018 as first-line therapy for patients with untreated systemic ALCL and other CD30-expressing subtypes (≥1% CD30 expression), including PTCL-NOS and nTFHL-AI.[19] The NCCN therefore included BV-CHP as a preferred first-line treatment option for CD30-positive T-cell lymphomas in its guidelines.[9] Our patient rapidly achieved PET negativity after only two cycles of BV-CHP treatment, enabling subsequent successful auto-SCT. PET negativity was maintained for almost 2 years. Although this response did not precisely mirror clinical trial outcomes, it underscores the efficacy of BV-CHP as frontline therapy in combination with consolidating SCT.

Bendamustine, a bifunctional molecule with alkylating activity and antimetabolic properties, showed a high response rate in r/r PTCL both as monotherapy and in combination with BV (B-BV).[20–22] It has proven to be particularly effective in nTFHL-AI patients.[21] Apparently, previous treatment with BV alone does not seem to affect the efficacy of B-BV. In a study involving nine patients previously treated with BV as monotherapy or in combination with chemotherapy (gemcitabine and vinorelbine), five patients responded to B-BV therapy, with four of them achieving a CR; interestingly, two of these patients were originally refractory to BV.[20] Unfortunately, this treatment regimen was not suitable for our patient and disease progression occurred after only three cycles of B-BV. Additional therapy with an intensive ICE-chemotherapy regimen was initially successful, but then the malignant disease progressed because the treatment was postponed due to prolonged SARS-CoV2 infection. At the end, belinostat therapy induced a response sufficient to allow the patient to receive an allo-SCT.

Belinostat is a hydroxamic acid-derived pan-HDAC inhibitor that targets Class I, II and IV HDAC, in contrast to romidepsin and chidamide HDACi, which are selective inhibitors targeting specific HDAC isoforms.[8] It is assumed that a broader spectrum of inhibition leads to better efficacy.[23] Belinostat prevents the growth of tumor cells by inducing cell cycle arrest and apoptosis. In addition, inhibition of HDAC also causes histone acetylation, which leads to an increased expression of tumor suppressor genes.[24]

In 2014, the FDA approval of belinostat for the treatment of r/r PTCL after at least one line of therapy was based on results of the phase II BELIEF study. Significantly higher response rates were obtained for nTFHL-AI than for other PTCL subtypes (ORR, 45.5% vs. 25.8%, respectively).[12,25] These study data therefore suggest that nTFHL may respond better to HDACis than other PTCL entities.

In the current 5th edition of the WHO lymphoma classification, nodal T-cell lymphomas with T-follicular helper (TFH) phenotype are grouped into an umbrella category based on clinical and immunophenotypic overlap, plasticity, as well as similar TFH gene expression signature and mutational profiles.[3] The so-called group of "nodal TFH cell lymphoma (nTFHL)" includes the entities nTFHL, angioimmunoblastic-type (nTFHL-AI), nTFHL, follicular-type (nTFHL-F) and nTFHL, not otherwise specified (nTFHL-NOS). These entities share the same genetic alterations such as TET2, IDH2, DNMT3A, RHOA and CD28 mutations, as well as gene fusions such as ITK-SYK or CTLA4-CD28, and express at least two TFH-related antigens, including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP and CCR5.[26] Retrospective studies have shown that TFH phenotype is an independent predictor of response to HDACi in PTCL ($p = 0.0035$) and that the use of HDACi led to successful SCT in approximately 18% of TFH patients.[27] Although statistical considerations so far preclude a definite conclusion, HDACi may have a higher activity in PTCLs with TFH phenotype compared to PTCLs without TFH phenotype and may contribute to the definition of subtype-specific therapy.[9,27]

Referring to the case report described here, in our heavily pretreated nTFHL-AI patient, CR was obtained after only four cycles of belinostat treatment, which enabled the successful implementation of a familial allo-SCT. There is growing evidence that belinostat has a high therapeutic potential in highly refractory disease settings and thus helps bridging to consolidative HSCT. For instance, a recently published case report of a young patient with heavily pretreated r/r nTFHL-AI impressively described the successful use of belinostat enabling allo-SCT. In this case, the patient achieved complete hematologic response that lasted for at least 2 years at the time this case report was written.[28] A sub-analysis of the BELIEF study also showed that 12 of 120 patients examined were able to receive HSCT following belinostat therapy, including two patients with nTFHL-AI.[29]

The safety of belinostat has been investigated in several clinical trials which confirmed its acceptable safety profile.[11,30,31] In a systemic study including 144 PTCL patients previously treated with belinostat, the most common adverse events were fatigue (35.0%), nausea (42.8%) and vomiting (28.5%), while grade 3/4 hematologic toxicities were comparatively rare (6.4%).[31]

This case report underlines the challenges that clinicians and patients face in the treatment of r/r PTCL. Not least, unexpected complications such as a SARS-CoV2 infection can hinder the treatment. Despite the complexity of the disease, sustained complete response was achieved in our patient with belinostat followed by an allo-SCT. This underlines the potential of HDACi as a salvage therapy for r/r PTCLs and offers a new attractive therapeutic option. Belinostat is currently being tested as a combination therapy which may thus achieve even a greater efficacy and enable its use in earlier lines of therapy. Promising results have already been shown in a phase I for newly diagnosed PTCLs: the addition of belinostat to CHOP (Bel-CHOP) achieved an ORR of 86%, with a tolerable safety profile.[32] The phase III CRESCENDO trial (NCT06072131) is currently investigating the efficacy and safety of Bel-CHOP—as well as pralatrexate plus CHOP—compared to CHOP alone in untreated PTCL patients. These further studies and clinical experience will help to fully clarify the role of belinostat in the treatment of PTCL, as well as its impact on long-term remission and survival outcomes.

4 | CONCLUSION

nTFHL-AI is a difficult-to-treat hematological malignancy, with a high potential of relapse upon first- or second-line treatments. HTSC represents a possibility for cure but only few patients are eligible. The presented case illustrates the clinical efficacy of belinostat by achieving sustained complete hematologic response in a heavily pretreated patient with relapsed nTFHL-AI, with acceptable safety profile. Following belinostat therapy, the patient was able to undergo an allo-SCT, which further contributed to the disease control and long-term remission. This underscores the potential of HDAC inhibition as a salvage therapy for r/r PTCL, building a bridge to HSCT.

AUTHOR CONTRIBUTIONS

Sigrid De Wilde: Conceptualization; data curation; methodology; project administration; resources; supervision; validation; writing – review and editing. **Carlos**

Graux: Investigation; methodology; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Sigrid De Wilde received honoraria from IDEOGEN AG (Switzerland). The co-author declares no conflict of interest regarding this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Not applicable.

CONSENT

This case report was published with written consent of the patient.

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