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Pembrolizumab-induced Remission After Failure of Axicabtagene Ciloleucel: Case Report and Literature Review

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Abstract. *Background: Failure after CD19-directed chimeric antigen receptor (CAR) T-cell therapy for patients with large B-cell B non-Hodgkin lymphoma, especially when it happens early, is an emerging clinical problem. There are no specific recommendations and therefore treatment of these patients remains empiricaI. Immune checkpoint inhibitors are becoming a therapeutic option for these patients. Case Report: We present a case of a primary mediastinal large B-cell lymphoma who experienced relapse 3.5 months after axicabtagene-ciloleucel therapy and received pembrolizumab. After four cycles of pembrolizumab, complete metabolic response was confirmed. Treatment was discontinued after the sixth cycle due to immune checkpoint inhibitor-related pneumonitis. The disease remains in remission 8 months after the last pembrolizumab dose. We propose mechanisms of action and optimal duration of pembrolizumab treatment in this setting. Finally, we review the existing literature on the sequential administration of CD19-directed CAR T-cell therapy and immune checkpoint inhibitors. Conclusion: Immune checkpoint inhibitors are a promising treatment option for patients after failure of CD19-directed CAR-T cell therapy.*

Primary mediastinal large B-cell lymphoma (PMLBCL) is a rare subtype of B-cell non-Hodgkin lymphoma that affects mainly younger patients (1). Treatment outcomes are favorable either with first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) usually with radiotherapy (2, 3) or with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) usually without radiotherapy (4), with associated 5-year event-free survival >75-85% and 5-year overall survival >85-90% (3, 4).

Despite these favorable responses, relapsed or refractory cases occur either during treatment or shortly after its completion (5). As in diffuse large B-cell lymphoma, salvage chemotherapy followed by autologous stem cell transplant is the standard of care (6) but in many patients the disease is chemorefractory and the outcome of these patients was generally very poor until recently (6, 7). Among therapeutic approaches for PMLBCL after a second relapse, only the programmed cell death-1 (PD1) inhibitor pembrolizumab and CD19-directed chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel (Axi-Cel) have commercial authorization (the former in the USA and the latter in the USA and EU).

PMLBCL presents frequent amplification and translocation events at the 9p24.1 locus, resulting in tumor expression of the PD1 ligands, PD-L1 and PD-L2 (8). In the KEYNOTE-170 trial, which enrolled patients with relapsed/refractory PMLBCL after at least two treatment lines, pembrolizumab at the dose of 200 mg every 3 weeks provided a 45% overall response rate (ORR), with 11% complete response (CR) (8). In the ZUMA-1 trial that evaluated Axi-Cel, in patients with refractory LBCL, eight patients with PMLBCL were included, with no specific information on the outcome of this subgroup (9). However, for the combined PMLBCL and transformed follicular lymphoma subgroup (24 patients), the ORR was 85% with 70% CR. Even long-term remissions were observed, with a 2-year progression-free survival rate of 39% in the ZUMA-1 trial (9). Another CAR T-cell product, tisagenlecleucel, has

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also been approved in the USA and EU for patients with relapsed/refractory LBCL after at least two prior treatment lines, having shown ORR of 52%, including 40% CR and 49% overall survival probability at 12 months for all patients who received an infusion (10).

For patients that experience relapse of LBCL after CAR T-cell therapy, the therapeutic landscape is generally ambiguous. Some existing data show that patients with early relapses (<3 months after CAR T-cell infusion) have very poor outcome, while those with late-onset relapses (>3 months after CAR T-cell infusion) have more promising outcomes (11). Among the treatment strategies that have been used in relapse after CAR T-cell therapy are allogeneic bone marrow transplantation, radiation, chemotherapy, lenalidomide and immune checkpoint inhibitors (11).

Relapses after CD19-directed CAR T-cell therapy may be CD19-positive or -negative (12, 13). CD19-positive relapses are mainly due to early CAR T-cell loss (*i.e.,* T-cell exhaustion), which can be the result of an overactivated PD1–PDL1 pathway (14). There are emerging data showing a possible synergistic effect of immune checkpoint inhibitors and residual CAR T-cells in cases of relapse in LBCL and B-acute lymphoblastic leukemia (15, 16).

We present a case of refractory PMLBCL in a female patient who experienced relapse after initial response to CAR T-cell therapy with Axi-Cel and achieved complete metabolic remission after the administration of pembrolizumab. Moreover, we review the existing relevant literature and speculate on the most appropriate time-point for the sequential administration of CD19-directed CAR T-cell and immune checkpoint inhibitor therapy.

Case Report

A 41-year-old female patient was diagnosed with PMLBCL after a bronchoscopically acquired biopsy of a mediastinal mass measuring 8×3 cm. The patient had presented severe pain at the left hip a month earlier, for which she underwent whole-body computed tomography (CT). In addition to the mediastinal mass, CT revealed a lytic lesion of the left femoral head, a non-measurable lesion next to the third sacral vertebra, a lesion next to the second rib-sternal junction (2.9×2 cm) and a mass next to the pancreatic head (3.6×3.3 cm). The patient also had evening fever (38˚C). The immunohistochemistry of the biopsy showed that the tumor was $CD20^+$, $CD30^+$ (30% of the cells), $BCL2^-$, $BCL6^-$, $MUM1^-$, and had a Ki67 index of 80%. Immunohistochemistry for PD1 expression was strongly positive. Fluorescent *in situ* hybridization examination for rearrangements of 9p24.1, where the genes for the two PD ligands are located, was also positive. After bronchoscopy, the patient developed thrombosis of the left superior vena cava and was placed on full anticoagulation with fractionated heparin and started pre-phase chemotherapy with dexamethasone and cyclophosphamide. Four days later, the patient presented with 'acute abdomen'. The surgical findings were consistent with duodenal perforation by a bulky nodal mass, which was pathologically proven to be PMLBCL. The patient received monotherapy with rituximab, with some improvement in her clinical condition (defervescence and pain amelioration). A week later she started the R-CHOP-21 combination. She received six cycles, while peripheral blood stem cell collection for a subsequent autologous stem cell transplant took place after the fourth cycle. CT after the end of R-CHOP therapy showed less than partial remission according to Cheson 2007 criteria (17) (less than 50% reduction of the baseline lesions) and positron-emission tomography (PET) was consistent with a Deauville score of 5 according to the Lugano 2014 guidelines (18), as the mediastinal lesion, the peri-pancreatic mass and the lesion of the left femoral head had maximum standardized ^{18}F-fluorodeoxyglucose uptake (SUVmax) values of 36, 28 and 27.5, respectively. There were several other areas with metabolic uptake substantially greater than that of the liver.

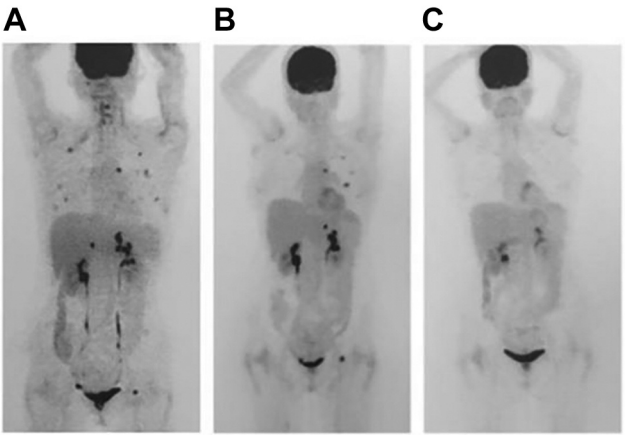

Figure 1. *Positron-emission tomography–computed tomography at 3.5 (A) and 5 (B) months after the CD19-directed chimeric antigen receptor T-cell infusion and after the fourth cycle of pembrolizumab therapy (C).*

The patient subsequently received salvage therapy with 2 cycles of R-ESHAP (rituximab, etoposide, doxorubicin, aracytine and prednisolone) with no response. Meanwhile, a new subcutaneous lesion had appeared at the level of the upper part of the sternum. A new biopsy confirmed PMLBCL. The patient again developed fever and severe pain of the left hip causing difficulty in walking. Combination therapy of polatuzumab vedotin with bendamustine and rituximab (Pola-BR) was then given for six cycles, with improvement of the patient's quality of life but with no impact on CT and PET-CT findings.

The patient was subsequently referred to a qualified CAR T-cell center in Germany to receive the Axi-Cel product. After the Axi-Cell infusion the patient developed grade 4 cytokine

release syndrome and immune effector-cell neurotoxicity syndrome, which were effectively treated. Fourty-eight days after Axi-Cel infusion, disease evaluation with CT and PET-CT revealed a CR. PET-CT 2 months later revealed new metabolically active lesions in mediastinal, pararenal and renal areas, with maximum diameter <1 cm and SUVmax of 10, 8.2 and 11.5, respectively (Deauville score 5) (Figure 1A). The patient was again referred to his home center for new treatment having progressive disease after Axi-Cel. CAR T-cells were still detected in the peripheral blood. On the patient's return to Greece, 5 months after CAR T-cell infusion, peripheral blood immunophenotyping was performed, which showed profound B-cell aplasia, a pharmacodynamic marker of functional CAR-T persistence (19, 20). PET-CT again showed the new metabolic lesions to be more or less unchanged (Figure 1B). We decided to treat the patient with the (off-label for Europe), immune checkpoint inhibitor pembrolizumab at a dose of 200 mg every 3 weeks until progression or unacceptable toxicity. After the fourth cycle of pembrolizumab, PET-CT revealed complete metabolic remission (Figure 1C), again with profound B-cell aplasia in peripheral blood. After the sixth cycle of pembrolizumab, the patient presented severe dyspnea on exertion. A chest CT showed ground-glass morphology in both upper lung lobes. Several bronchoscopic cultures were completely negative for specific pathogens and PET-CT again showed metabolic remission, with mild metabolic uptake (SUVmax=2.6) at the sites of the ground-glass morphology. The diagnosis of immune checkpoint inhibitor-related pneumonitis was established (21). The patient was treated with 0.5 mg/kg prednisolone and 2 weeks later dyspnea and oxygen need subsided and slow tapering of prednisolone started. Pembrolizumab infusions were held, and the patient was placed under close monitoring with frequent PET-CT. The disease remains in metabolic CR 16 months after Axi-Cel infusion and 8 months after the last infusion of pembrolizumab.

Discussion

The treatment of relapses after CAR T-cell therapy, especially when they occur early, as in this case, is usually unsuccessful, so that these patients comprise a current unmet medical need (11). In many cases, the reason for relapse can be CAR T-cell exhaustion after an initial expansion, which may be attributed partly to PD1–PDL1 pathway interaction (14). It has been documented that the checkpoint proteins PD1 and PD-L1 are expressed on CAR T-cells and in the tumor microenvironment and are up-regulated after CAR T-cell infusion (22).

Our patient experienced metabolic relapse after metabolic CR at 3.5 months from the CD19-directed CAR T-cell infusion, however, with CAR T-cells still present, as was concluded from

Table I. *Clinical trials with sequential CD19-directed chimeric antigen receptor (CAR) T-cell and immune checkpoint inhibitor (ICI) therapy.*

Type of trial, disease (Ref)	Trial status	No. of patients	Age range, years	Type of CAR T-cell therapy	ICI therapy	Reason for ICI initiation	Interval between CAR T- cell and ICI therapy
Investigator initiated, B-ALL (15)	Terminated	14	4-17	Tisa-cel or CTL119	Pembrolizumab (n=13) or nivolumab (n=1) until progression or unacceptable toxicity, doses not mentioned	Repeated early CAR T-cell loss (group 1=6) or partial/no response to CAR T-cell therapy (group 2=8)	2-7 Weeks
Phase I/II (NCT02650999), R/R DLBCL and FL (16)	Active-not recruiting	11 R/R DLBCL 1 R/R FL	30-78	Tisa-cel or CTL119	200 mg Pembrolizumab *i.v.* q3w until progression or unacceptable toxicity	During early progression (non-responders) (group 1=8) or late relapse (group 2=4)	Median (range)=3.3 (0.4-42.8) months
Phase I (NCT02706405), R/R aggressive NHL (23)	Active recruitment	15	32-69	JCAR014	Durvalumab, escalating doses up to 10 cycles	Scheduled infusions without evidence of CAR T-cell failure	Scheduled infusion between 1 day before to 28 days after CAR T-cell infusion
Phase I (NCT02926833)-ZUMA-6, R/R DLBCL (24)	Active, not recruiting	12	30-66	Axi-Cel	1200 mg Atezolizumab *i.v.* for four 21-day cycles	Scheduled infusions without evidence of CAR T-cell failure	Starting on day 14 or 21, or 1 day post CAR T-cell infusion
Cohort study (25)	Retrospective	11	26-70	CD19 CAR-T cells (Creative Biolab)	Single dose of 3 mg/kg nivolumab	Scheduled infusion without evidence of CAR T-cell failure	Day 3 post n CAR T-cell infusio

Axi-Cel: Axicabtagene ciloleucel; B-ALL: B acute lymphoblastic leukemia; CAR: chimeric antigen receptor; CD: cluster of differentiation; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; NHL: non Hodgkin lymphoma; R/R: relapsed/refractory; Tica-cel: tisagenlecleucel.

Table II. *Responses and adverse events of clinical trials with sequential CD19-directed chimeric antigen receptor T-cell and immune checkpoint inhibitor therapy.*

Type of trial, disease (Ref)	Disease (Ref)	Response	Adverse events
Investigator initiated, B-ALL (15)	B-ALL (15)	Group 1: 3/6 re-established B-cell aplasia, no PD Group 2: 4/8 responded (2 CRs and 2 PRs), all had bulky extramedullary disease	CRS symptoms: n=3 Cytopenia, grade 3/4: n=4 Acute pancreatitis: n=1 Hypothyroidism: n=1 Arthralgia: n=1 Urticaria: n=1
Phase I/II (NCT02650999), R/R DLBCL and FL (16)	R/R DLBCL and FL (16)	1 CR, 2 PRs, 1 SD, 7 PDs 9/12 Patients had a re-expansion peak in peripheral blood CAR T-celIs	Neutropenia, grade 3/4: n=3 CRS, grade 3: n=1 Infusion reaction, grade 2: n=1, Fever, grade 1/2: n=2 Fatigue, grade 1/2: n=2 Pleural effusion, grade 1: n=1 Arthralgia, grade 1: n=1 CMV infection, unrelated: grade 4: n=1
Phase I (NCT02706405), R/R aggressive NHL (23)	R/R aggressive NHL (23)	13 Evaluable patients: ORR=50% (5 CRs and 1 PR)→relapse in 1 patient with CR Continued SD and evidence of regression in 4 more patients	CRS, grade 1/2: n=4; grade 4: n=1 Neurotoxicity, grade 1: n=1
Phase I (NCT02926833)-ZUMA-6, R/R DLBCL (24)	R/R DLBCL (24)	10 Evaluable patients: ORR=90% (6 CRs, 3 PRs) CAR T-cell expansion >2-fold higher than in patients treated with Axi-Cel alone (ZUMA1)	Anemia, grade 3: n=9 Encephalopathy, grade 3: n=5 Neutropenia, grade 3/4: n=5 CRS, grade 3: n=3 Neurotoxicity, grade 3: n=6
Cohort study (25)	Cohort study (25)	9/11 Patients responded, with 5 CRs Median PFS=6 months	CRS, grades 1/2: n=9

Axi-Cel: Axicabtagene ciloleucel; B-ALL: B acute lymphoblastic leukemia; CAR: chimeric antigen receptor; CMV: cytomegalovirus; CR: complete response; CRS: cytokine-release syndrome; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; NHL: non Hodgkin lymphoma; ORR: overall response rate; PD: progressive disease; PR: partial response; R/R: relapsed/refractory; SD: stable disease.

the profound B-cell aplasia (19, 20). The relapse was metabolic as well as clinical (Figure 1A and B), as areas of new lymph node disease appeared in the CT scans (17,18).

The favorable outcome of pembrolizumab treatment in this patient can be explained by two different mechanisms. Firstly, PD1 inhibition by pembrolizumab apparently managed to overcome the CAR T-cell exhaustion caused by an overactivated checkpoint pathway, leading to increased numbers of circulating CAR T-cells and re-induction of metabolic CR. However, it should be noted that actual CAR T-cell measurements were not performed. However, continuing profound B-cell aplasia was confirmed. The second mechanism might stem from the fact that pembrolizumab induces responses in a considerable number of patients with relapsed/refractory PMLBCL especially in the setting of increased PD1/PDL1 expression (8). In our patient's case, PD-L1 expression and 9p24.1 rearrangement were strongly positive in the diagnostic tissue. Our patient received only six cycles of pembrolizumab and achieved complete metabolic remission even after the fourth cycle. The treatment with pembrolizumab was discontinued due to pneumonitis, however, the patient remained in metabolic CR for at least 8 months after discontinuation. This favorable outcome with brief pembrolizumab treatment can be attributed to a synergistic effect of the two mechanisms of pembrolizumab action described above.

There are several data emerging from clinical trials that support our findings, which also confirm that PD1/PDL1 pathway inhibition after CD19-directed CAR T-cell therapy may improve the function and persistence of CAR T-cells (15, 16). Table I and Table II summarize the most important research data for sequential CD19-directed CAR T-cell and immune checkpoint-inhibitor therapy (15, 16, 23-25). In some of these trials, the immune checkpoint inhibitor was added only after clinical relapse or in the case of proven CAR T-cell exhaustion (15, 16), while in other, immune checkpoint inhibitor infusion was scheduled at specific time-points after or shortly before the CAR T-cell infusion (23-25). Some of these trials are still ongoing.

The data from Table I and Table II, as well as our experience with our patient with PMLBCL, indicate that the sequential infusion of a PD1 inhibitor after CD19-directed

CAR T-cell therapy may overcome disease relapse or resistance in a considerable number of patients. In particular, the subgroup of patients with PMLBCL who experience relapse after CD19-directed CAR T-cell therapy may enjoy the most favorable outcomes.

Regarding the additive drug-specific toxicity of this treatment strategy, such by the immune checkpoint inhibitor-related pneumonitis of our patient, perhaps a short-term infusion schedule (*e.g.,* for 4-5 cycles) might induce CD19 CAR T-cell re-expansion without impairing efficacy. Moreover, immune checkpoint inhibitor therapy in cases of lymphoma relapse after CD19-directed CAR T-cell therapy might be more efficacious as a pre-emptive method (not in the setting of relapse or failure of CD19 CAR T-cell expansion) in specific subgroups of patients with high-risk characteristics (*e.g.,* bulky disease) before CAR T-cell infusion. Consequently, sequential infusion with CD19-directed CAR T-cell and immune checkpoint inhibitor in patients with LBCL, and among them those with PMLBCL, deserves further clinical investigation with larger prospective clinical trials.

Conflicts of Interest

All Authors have nothing to disclose.

Authors' Contributions

All Authors contributed to the writing of the article.

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