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LETTER

Parkinson-like neurotoxicity in female patients treated with idecabtagene-vicleucel

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Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) are two BCMA-directed CAR T-cells approved for the treatment of relapsed or refractory multiple myeloma. Similar to CD19-directed CAR T-cells, acute adverse events may occur after BCMA-directed CAR T-cells, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). However, a new type of neurotoxicity has been recently reported in patients treated with BCMA-directed CAR T-cells, the so-called movement and neurocognitive toxicity (MNT). Common features include late onset of Parkinson-like symptoms such as tremor, bradykinesia, and neurocognitive disorder. Only 10 cases of MNT occurring after BCMA-directed CAR T-cells have been reported so far (Table 1). The symptoms appeared with a median time of 36 days (range, 14–914 days). Interestingly, all cases occurred in male patients and after cilta-cel except for one patient who had been treated with ide-cel.[4] MNT has been associated with high expansion and persistence of circulating CAR T-cells, cerebrospinal fluid infiltration by CAR T-cells, and no clear response to levodopa. Autopsy report from a patient who died shortly after presenting with MNT showed a T-cell infiltrate in the periventricular region of the basal ganglia as well as BCMA expression in the basal ganglia, suggesting an on-target off-tumor toxicity.[1] BCMA expression was also found on basal ganglia cells of healthy subjects.[1] Potential risk factors of MNT include high tumor burden at baseline before the start of lymphodepletion, grade ≥2 CRS, occurrence of ICANS, high CAR T-cell expansion, and prolonged persistence.[1] Management of this new and rare toxicity remains poorly defined. Corticosteroids, systemic chemotherapy, anakinra, intrathecal injections of cytarabine and steroids, IV Ig, and plasmaspharesis have been tested without clear benefit. Most patients experience mild or no improvement of their symptoms. In some patients, symptoms worsen and may lead to death.

Here, we report the case of two female patients who developed parkinsonism after ide-cel infusion.

Patient 1 is a 74-year-old woman who had been diagnosed with monoclonal gammopathy of unknown significance in 2003, which progressed to multiple myeloma in 2009. Before undergoing CAR T-cell therapy, she had received 11 prior lines of therapy including chemotherapy, IMIDs, proteasome inhibitors, daratumumab, and lastly talquetamab, a CD3/GPRC5D bispecific antibody. She was offered CAR T-cell therapy after developing lytic bone lesions while being treated with talquetamab. She received bridging therapy with Selinexor, which allowed partial metabolic response. After ide-cel infusion, she developed grade 1 CRS on Day 2 and no ICANS. She did not require treatment with tocilizumab nor dexamethasone. She was discharged on Day 10 postinfusion.

Immunofixation was negative 1 and 3 months after infusion (monoclonal spike was 3.7 g/L at baseline). [18F] FDG PET/CT evaluation after ide-cel infusion showed a partial response at 1 month and a complete response at 3 months.

At Day 36 after CAR T-cell infusion, the patient developed a discrete tremor along with mild psychomotor retardation. Cognitive and motor impairment worsened requiring hospitalization on Day 49 post CAR T-cell infusion. Clinically, she presented with Parkinson-like symptoms including asymmetric tremor, hypomimia, and rigidity. The symptoms worsened after a few days with severe rigidity, akinesia, and postural instability.

CAR T-cell monitoring showed high expansion and persistence of CAR T-cells with 92 CAR T-cells/µL at Day 7 and 374/µL at Day 35, by flow cytometry (Figure 1A). Similar to what has been previously reported, immunophenotyping of CD4 and CD8 CAR T-cells at Day 35 revealed that most CAR T-cells were EM-like (CD45RA−CCR7−), with a small proportion of EMRA-like CAR T-cells (CD45RA+CCR7−).[6] Brain MRI showed right-predominant bipallidal signal abnormalities of small extent, evolving in diffusion restriction with FLAIR hypersignal. Similar to other cases previously reported, ^{123}I-FP-CIT SPECT/CT scan was normal, suggesting integrity of the presynaptic dopaminergic transporters. [18F]FDG PET/CT showed decreased [18F]FDG activity in both striata (Figure 1B,C). CSF examination showed hyperproteinorrachia (0.83 g/L), normoglycorachia (4.62 mmol/L) with 23/mm^3 red blood cells (RBC) and 7/mm^3 leukocytes. By flow cytometry, 94% of lymphocytes were CAR T-cells.

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TABLE 1 Characteristics of patients presenting MNT after BCMA-directed CAR T-cells. (continued on next page)

Reference	Couturier et al. 2024 (current study)	Couturier et al. 2024 (current study)	Van Oekelen et al.,[1] 2021	Cohen et al.[2] 2022					Martin et al.,[3] 2022	Karschnia et al.,[4] 2023		San-Miguel et al.,[5] 2023
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
CAR T-cell (trial)	Ide-cel	Ide-cel	Cilta-cel	Cilta-cel (CARTITUDE 1)	Cilta-cel (CARTITUDE 1)	Cilta-cel (CARTITUDE 1)	Cilta-cel (CARTITUDE 1)	Cilta-cel (CARTITUDE 2)	Cilta-cel (CARTITUDE 1)	Cilta-cel	Ide-cel	Cilta-cel (CARTITUDE 4)
Sex	Female	Female	Male	Male	Male	Male	Male	Male	Not reported	Male	Not reported	Male
CRS, grade	1	1	3	≥2	≥2	≥2	≥2	4	2	2	Not reported	Grade 2
ICANS, grade	0	0	0	4 patients out of 5 had ICANS					3	2	Not reported	Not reported
Symptoms	Psychomotor retardation, apathy, executive dysfunction, asymmetric tremor, hypomimia, bradykinesia, rigidity with cogwheel phenomenon, gait instability	Asymmetric rigidity and tremor Apathy, executive and mnesic dysfunction, hypomimia	Fatigue, slow gait, psychomotor retardation, bradykinesia, hypomimia, micrographia, asymmetric tremor, impaired short-term memory	Bradykinesia, cogwheel rigidity, dysgraphia, dyskinesia, gait disturbance, resting tremor, memory impairment, psychomotor retardation, reduced facial expression				Micrographia, bradykinesia, rigidity, bradyphrenia, flat effect, apathy, gait disorder, cognitive impairment	Cognitive slowing, gait instability, neuropathy, tremor	Difficulty walking, neurocognitive impairment, inattention, masked facies, hypophonia, intention tremor, stooped posture.	Confusion, bradykinesia, increased muscle tone	Not reported
Time from infusion to onset of symptoms	Day 36	Day 33	Day 101	Median, range: 27 days (14–108)				Day 38	Day 914	Day 19	Day 22	Day 85
DATscan	Normal	Normal	Normal	Not reported				Not reported	Not reported	Not reported	Not reported	Not reported
Brain FDG-PET	Hypometabolism of the basal ganglia and of the heads of the caudate nuclei and the anterior part of the putamen, as well as associative cortex involvement, with hypometabolism of the medial frontal and temporal regions	Not reported	Decreased uptake in the caudate nucleus bilaterally	One patient had brain FDG-PET scan which showed hypometabolism in basal ganglia				Not reported	Not reported	Mild hypometabolism in the frontal lobe, anterior cingulate gyri and to a lesser degree, parietal lobes	Decreased uptake in the bilateral caudate nuclei	Not reported

TABLE 1 (Continued)

Reference	Couturier et al. 2024 (current study)	Couturier et al. 2024 (current study)	Van Oekelen et al.,[1] 2021	Cohen et al.[2] 2022					Martin et al.,[3] 2022	Karschnia et al.,[4] 2023		San-Miguel et al.,[5] 2023
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Brain MRI	Right-predominant biballidal signal anomalies of small extent, evolving in diffusion restriction with FLAIR hypersignal	Pre-existing periventricular foci of T2/FLAIR signal and pre-existing left parietal cortico-subcortical sequelae	Small pre-existing foci of T2/FLAIR signal hyperintensity scattered throughout the periventrical and subcortical matter	One patient had brain magnetic resonance imaging: no significant abnormalities				Not reported	Not reported	No structural abnormality or abnormal regions of restricted diffusion, contrast enhancement, or suggestion of acute or evolving structural pathologic features	No specific acute MRI abnormalities	Not reported
Response to antiparkinsonism drugs	No improvement	No significant improvement	No improvement	Not reported				Not reported	No improvement	Not reported	No improvement, worsening of symptoms	Not reported
Etiologic treatment	Fludarabine, Intrathecal MTX/cytarabine/hydrocortisone	Fludarabine, Intrathecal MTX/cytarabine/hydrocortisone	Cyclophosphamide, IT cytarabin + IT hydrocortisone	Not reported				High dose MP, IgIV, Plasmapheresis	None	Dexamethasone, anakinra, cyclophosphamide	Steroids, anakinra	Not reported
Response to etiologic treatment	Mild improvement	Mild improvement	Not evaluated	1 recovered or resolved 2 not recovered or not resolved 1 died				Mild improvement	Stable symptoms	Improvement of gait, psychomotor slowing, inattentiveness and hypomimia, residual intention tremor	No improvement, worsening of symptoms	Not reported
Outcome	Alive at last follow-up (Day 121)	Alive at last follow-up (Day 77)	Death from neutropenic fever	Death from lung abscess	Death from septic shock	Death from neurotoxicity	Alive at last follow-up	Alive at last follow-up	Alive at last follow-up	Alive at last follow-up	Death from bacterial and fungal sepsis	Not reported

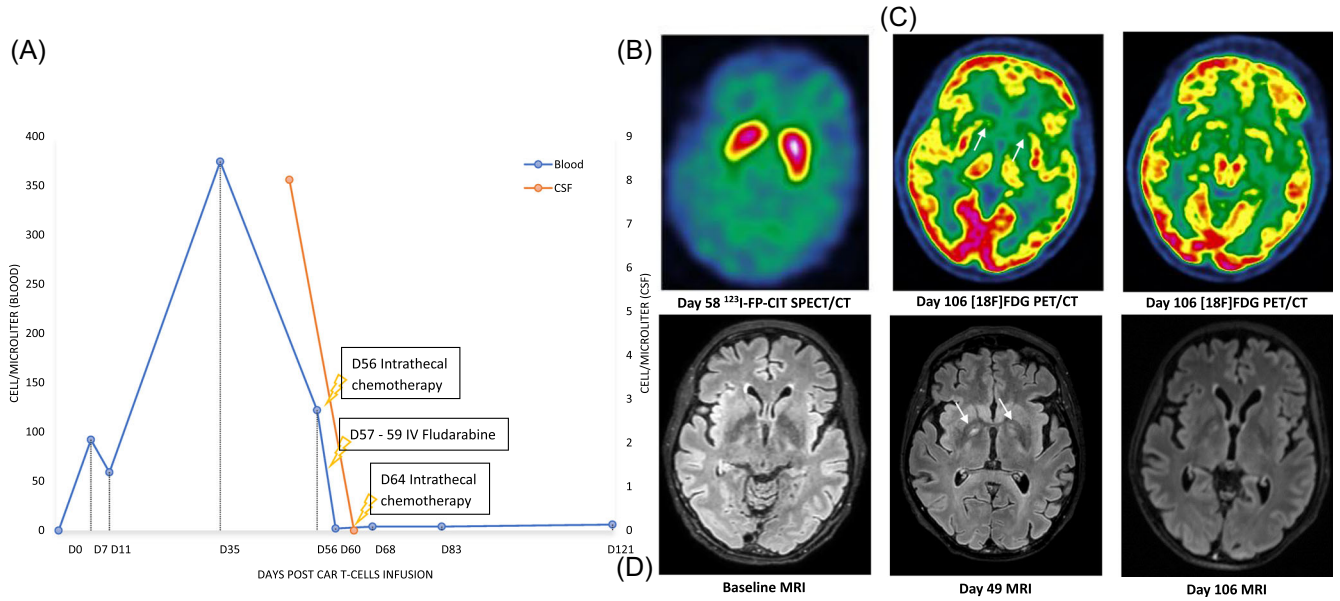

FIGURE 1 Clinical, biological, and radiological findings related to neurological toxicity, patient 1. (A) Circulating CAR T-cells over time, measured by flow cytometry, and correlation to motor and cognitive symptoms. IV Fludarabine allowed a steep decrease in circulating CAR T-cells. (B) 123I-FP-CIT SPECT/CT images showing no presynaptic dopaminergic denervation. (C) [18F]FDG PET/CT images with decreased [18F]FDG activity in both striata (arrows). (D) Repeated axial brain resonance imaging (MRI) with fluid-attenuated inversion recovery (FLAIR) showing asymmetric bipallidal signal abnormalities (arrows), decreasing over time.

On Day 56, while her neurologic condition continued to worsen, the patient was started on dopamine agonists and received systemic chemotherapy with fludarabine 30 mg/m²/day for 3 days as well as two intrathecal injections of methotrexate, aracytine, and methylprednisolone. Upon treatment, the patient showed rapid clinical improvement and was able to recover walking ability and sufficient autonomy to be discharged from the hospital on Day 88. CSF examination on Day 14 from the first intrathecal chemotherapy and Day 8 of IV Fludarabine showed complete clearance of CAR T-cells. Blood analysis at day 60 showed almost complete clearance of circulating CAR T-cells, down to 2 cells/µL (Figure 1A).

L-dopa test being negative, levodopa/carbidopa was progressively discontinued. The symptoms did not worsen after withdrawal of carbidopa/levodopa. Despite significant improvement, the patient did not fully recover and was still experiencing attitude and rest tremor of the four limbs with left-side predominance, severe rigidity, and bradykinesia as well as persisting apathy and dysexecutive symptomatology 3 months after fludarabine treatment. Follow-up brain MRI at day 118 revealed a marked reduction in diffusion hypersignal and T2 bi-pallidal signal anomalies predominantly on the right, although to a less marked extent (Figure 1D).

Patient 2 is a 73-year-old woman with penta-refractory multiple myeloma, first diagnosed in 2019. Following ide-cel treatment, she developed self-resolving grade 1 CRS and no ICANS, allowing discharge from the hospital on Day 12 after CAR T-cell infusion. The peak of CAR T-cell expansion was 261/µL at Day 10. At 1 month evaluation, [18F]FDG PET/CT showed a complete metabolic response while serum protein electrophoresis showed very good partial response with a monoclonal spike down to 4.8 g/L, against 44 g/L at baseline. Clinical assessment revealed the onset of Parkinson-like symptoms, including hypomimia, resting tremor, hypokinesia, and walking impairment. Neurologic evaluation found neurocognitive debilitation with severe apathy, and mnesic as well as executive difficulties. Lumbar puncture revealed lymphocytic meningitis, with 32% of lymphocytes being CAR T-cells as assessed by flow cytometry.

Brain MRI was unchanged compared to baseline, notably, there was no lesion of the basal ganglia. ^{123}I-FP-CIT SPECT/CT scan was normal. No significative improvement was observed after initiation of dopatherapy. The patient received a systemic chemotherapy with fludarabine 30 mg/m²/day for 3 days (from Day 42 to Day 44), and one intrathecal injection of methotrexate, aracytine, and methylprednisolone. This treatment induced a rapid and profound depletion of circulating CAR T-cells with less than 1 CAR T-cell/µL detectable at Day 75 of infusion. We observed a clinical, although partial, improvement with reduction of rigidity, hypokinesia, and tremor.

Despite successful depletion of CAR T-cells, none of the two patients experienced disease relapse/progression at last follow-up. Patient 1 remained in complete metabolic response at M6 with a negative immunofixation at M9. In patient 2, the monoclonal spike remained stable at 3.4 g/L at M3 versus 4.8 g/L before Fludarabine treatment.

These two cases have previously unreported features. First, to the best of our knowledge, these are the first reported cases of CAR T-cell induced-MNT occurring in female patients. Second, these are the second and third cases of MNT reported after ide-cel. Third, we were able to show for the first time abnormalities of the basal ganglia on brain MRI (patient 1), further supporting the pathophysiological mechanism associated with CAR T-cell-induced NRM neurotoxicity, explaining the lack of dopaminergic denervation and resistance to levodopa. Finally, we show for the first time that systemic fludarabine may be an effective treatment of MNT. Because MNT is thought to be due to the destruction of the basal ganglia by BCMA-directed CAR T-cells, we hypothesized that rapid depletion of CAR T-cells from the brain and CSF may be key to avoid irreversible neurologic damages. We chose to use fludarabine because it is a potent lymphodepleting chemotherapy which crosses the blood brain barrier.[7] The rapid clearance of

CAR T-cells from the CSF along with the clinical improvement supports this strategy.

Movement and neurocognitive toxicity is a rare but potentially severe adverse event occurring in patients treated with BCMA-directed CAR T-cells. This toxicity has mostly been described in male patients and after cilta-cel treatment, but may occur in female patients and after ide-cel, as reported here. However, the exact sex ratio and the proportion of cilta-cel vs ide-cel in MNT patients remain unknown because cases are likely to be underreported and there is no exhaustive data to determine the percentage of MNT among all treated patients (based on sex and treatment characteristics). Therefore, the diagnosis of MNT should not be excluded/influenced based on sex nor CAR T-cell product. Furthermore, current understanding of the pathophysiology suggests direct destruction of the basal ganglia by BCMA-directed CAR T-cells. This supports the need for rapid eradication of CAR T-cells from the brain which may be achieved with systemic lymphodepleting chemotherapy, such as cyclophosphamide or fludarabine. Physicians should be aware of this rare toxicity to allow early recognition and rapid intervention in order to limit the risk of irreversible neurologic damages.

AUTHOR CONTRIBUTIONS

Roch Houot and Audrey Couturier conceived and wrote the original article. Xavier Palard, Florence Lejeune, Frédérique Leh, Anne-Sophie Villoteau, Martine Escoffre, Oliver Decaux and Thierry Lamy reviewed and edited the article. Xavier Palard, Florence Lejeune, and Anne-Sophie Villoteau helped with research and investigation for the article.

CONFLICT OF INTEREST STATEMENT

Roch Houot received honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda, and Roche; and consultancy at Kite/Gilead, 63 Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte, Miltenyi. Olivier Decaux received honoraria from Janssen, Celgene/BMS, Amgen, Takeda, GSK, Sanofi, Abbvie, Roche, The Binding Site, Sebia, Menarini-Stemline, and Pfizer. The remaining authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Data will be shared upon request to the corresponding author.

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