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705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

CAR+ T-Cell Lymphoma Post Ciltacabtagene Autoleucel Therapy for Relapsed Refractory Multiple Myeloma

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Introduction: Rareevents of T-cell lymphoma (TCL) derived from CAR-T cells (2 cases) have been reported in patients receiving nonviral piggyBac transposon-based CAR-T therapy (Micklethwaite et al, *Blood*, 2021). Ciltacabtagene autoleucel (cilta-cel) is an anti-BCMA CAR-T therapy produced via conventional lentiviral transduction. In the randomized, phase 3 CARTITUDE-4 study (NCT04181827), cilta-cel significantly improved PFS (HR=0.26) vs standard of care in lenalidomide-refractory patients with multiple myeloma and 1-3 prior lines of therapy. We present the clinicogenomic characterization of a CARTITUDE-4 patient who developed a CAR+ TCL post cilta-cel.

Methods: Diagnostic and staging workup included biopsy analyses and FDG-PET scan. Presence of CAR+ cells in lymph node biopsy (LNB) was assessed by quantitative polymerase chain reaction (qPCR), in situ hybridization (ISH), and immunohistochemistry (IHC). Whole genome sequencing (WGS), transcriptome sequencing, whole exome sequencing (WES), T-cell receptor (TCR) sequencing, and genome-wide CAR integration analyses were conducted.

Results:A 51 y/o male patient received cilta-cel; CAR+ T cells in blood peaked 14 d post-infusion (77 cells/μL) and decreased to 3 cells/μL at d 92 post-infusion, when he achieved stringent complete response (sCR) and MRD negativity at 10^{-5}. At 5 mo post-infusion, a relatively rapidly growing erythematous nasofacial plaque developed. TCL was diagnosed based on facial lesion biopsy showing an infiltrate of atypical T cells positive for CD2 and CD3 but negative for CD4, CD8, CD7, CD56, ALK, EBER-ISH, TdT, CD30, and cytotoxic T cell markers. FDG-PET showed bilateral FDG-avid cervical lymphadenopathy, with similar T cell infiltrate in submandibular LNB. qPCR and ISH/IHC revealed 90-100% of LNB cells to be CAR+. At d 162 post-infusion (after TCL diagnosis but before TCL-directed chemotherapy) CAR+ T cells in blood had re-expanded, independent of BCMA antigen, to 378 cells/μL.

CAR integration analysis of LNB revealed a dominant insertion into the 3'UTR of *PBX2* (91.1% of total reads from all integration sites), suggesting tumor monoclonality. TCR sequencing (1.8×10^{-6} sensitivity) of LNB showed a monoclonal sequence in 91% of all T cells. Analysis of the drug product revealed the same unique TCR sequence from the monoclone at low frequency ($\sim2\times10^{-6}$), suggesting the presence of this clone in apheresis material.

WGS showed low overall mutational burden in the LNB (1.26 mutations/megabase) with 37 coding and 3286 non-coding variants, including 2 predicted loss-of-function *TET2* mutations; a *PTPRB* truncation; and a focal duplication involving the 5'UTR to intron 16 of *NFKB2*. No dominant mutational signatures or gross copy number changes were observed. WES of

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the LNB indicated that a *TET2* mutation (p.H1416R), which was not due to CAR insertion, was heterozygous and likely clonal. Targeted sequencing (0.5% sensitivity) of stored CD34+ cells and bone marrow aspirate collected from the patient 2 y earlier showed no abnormalities. Germline samples revealed the presence of a heterozygous *JAK3* variant (p.V722I) that has been described as an activating variant, implicated in TCL, and detected in germline samples from patients with antigen-induced TCL (Blombery et al, *Haematologica*, 2016).

The patient received CHOEP-21 (cyclophosphamide-doxorubicin-vincristine-prednisone-etoposide) and achieved metabolic CR but relapsed soon after treatment was stopped. Subsequent treatment with gemcitabine-dexamethasone-cisplatin-alemtuzumab was followed by consolidation with fludarabine plus melphalan and matched allogeneic stem cell transplant. He relapsed with cutaneous disease within 3 mo.

Conclusions: To our knowledge, this is the first case of CAR+ TCL occurring after infusion of a CAR-T therapy produced via lentiviral transduction (cilta-cel). This rare malignancy was potentially driven by genetic mutations (e.g., *TET2, NFKB2, PTPRB* and/or *JAK3*), some of which may have existed in the form of a clone with malignant potential before cilta-cel manufacturing (e.g., *TET2* p.H1416R and *JAK3* p.V722I variants). A potential contributory role of the CAR insertion in the 3′ untranslated region of *PBX2* to TCL development remains unclear and cannot be excluded at this time. Further investigation is needed to elucidate the differential contributions of these genomic factors to the etiology of this TCL case.

Disclosures Harrison: *Haemalogix:* Membership on an entity's Board of Directors or advisory committees; *Abbvie, Amgen, Celgene/BMS, GSK, Janssen Cilag, Novartis, F. Hoffmann-La Roche Ltd / Genentech, Inc., Eusa:* Speakers Bureau; *Abbvie, Amgen, Celgene/BMS, GSK, Janssen Cilag, Novartis, F. Hoffmann-La Roche Ltd / Genentech, Inc., Haemalogix, Eusa, Terumo BCT:* Honoraria; *Celgene/BMS, GSK, Janssen Cilag, Haemalogix:* Research Funding; *Abbvie, Amgen, Celgene/BMS, GSK, Janssen Cilag, Novartis, F. Hoffmann-La Roche Ltd / Genentech, Inc., Haemalogix, Eusa, Terumo BCT:* Consultancy. **Er:** *Roche:* Honoraria. **Li:** *Janssen R&D:* Current Employment, Current equity holder in publicly-traded company. **Lendvai:** *Janssen R&D:* Current Employment, Current holder of *stock options* in a privately-held company. **Schecter:** *Janssen:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties: Janssen. **Banerjee:** *Janssen:* Current Employment, Current holder of *stock options* in a privately-held company. **Roccia:** *Janssen:* Current Employment, Current equity holder in private company. **Foulk:** *Janssen:* Current Employment. **Gu:** *Johnson & Johnson:* Current Employment, Current equity holder in private company. **Smirnov:** *Janssen Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Slaughter:** *Janssen:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Lonardi:** *Janssen R&D:* Current Employment. **Lee:** *Johnson & Johnson:* Current Employment, Current equity holder in private company. **Marquez:** *Janssen R&D:* Current Employment, Current holder of *stock options* in a privately-held company, Divested equity in a private or publicly-traded company in the past 24 months. **Jadidi:** *Janssen:* Current Employment. **Costa Filho:** *Legend Biotech:* Current Employment, Current equity holder in publicly-traded company. **Patel:** *Legend Biotech, GSK, Freeline, BMS (spouse), AbbVie (spouse):* Current Employment, Current equity holder in publicly-traded company, Divested equity in a private or publicly-traded company in the past 24 months, Ended employment in the past 24 months. **Geng:** *Legend Biotech:* Current Employment. **Haynes:** *Bristol Meyers Squibb:* Research Funding; *Aculeus Therapeutics Pty Ltd:* Consultancy.

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