Society for Hematopathology

Webinar Q&A: October 14, 2026

"Severe Post–Cilta-cel Diarrhea: Enterocolitis, Immune Toxicity, or Lymphoproliferative Disorder?"

Speaker:
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1. **Question:** Can you please discuss the importance (or not) of T cell clonality in IEC-EC diagnosis? It is easier for my institution to investigate T cell clonality compared to camelid IHC (we do not have access to this IHC in our lab).
   Answer: In the absence of camelid IHC, I think the diagnosis of IEC-EC/LPD is very likely when the duodenum shows villous blunting, increased crypt apoptotic bodies, and a dense infiltrate of CD3+ cytotoxic T-cells in the lamina propria. I think this combination of findings in a patient who has received Cilta cel and has diarrhea would be reasonably managed as IEC-EC/LPD. Remember, the pretest probability of IEC-EC/LPD in this clinical scenario is already in the ballpark of 60-80%.

   As most labs have CD4 and CD8, I would definitely do those as well. Most cases will show a skewed CD4:CD8 ratio, which will provide further reassurance of the diagnosis. But we know there are cases with markedly increased camelid+ cells with a mixture of CD4+ and CD8+ cells. So I would not exclude IEC-EC/LPD on the basis of a mixed CD4:CD8 ratio. Additionally, I would not exclude IEC-EC/LPD on the basis of a negative clonality study. So CD4 and CD8 are helpful as they will be skewed in most cases. Similarly, clonality is going to be positive in most cases, but a negative clonality study does not exclude IEC-EC/LPD. So I would focus more on histologic features (villous blunting, high density of T cells with cytotoxic phenotype, skewed CD4:CD8 ratio) than doing clonality, but certainly clonality will not hurt unless a negative result incorrectly leads one to say a case is not IEC-EC/LPD.

2. **Question:** Is camelid immunogenic to human native immune system?
   Answer: Yes, anti-drug antibodies (ADAs) do form. ADAs commonly form after administration of biologics, so this is not surprising. Below is an excerpt from Alfar HR, Chen C, Lachacz E, Tang W and Zhang Y (2025) Clinical evidence of immunogenicity of CAR-T cell therapies and its implication in the clinical development of CAR-T drug products. Front. Immunol. 16:1512494. doi: 10.3389/fimmu.2025.1512494

"During the two main clinical studies of ciltacabtagene (CARTITUDE-1 and CARTITUDE-4), preexposure and post-exposure serum samples were collected from participating patients to assess the humoral immunogenicity before and after ciltacabtagene using a validated immunoassay to detect ADA against the extracellular BCMA-binding domain of ciltacabtagene (63). In the CARTITUDE-1 study, 19.6% (19 of 97 patients) were positive for treatment emerged ADA (67). In CARTITUDE-4 study, 21% of the patients (39 of 186 patients) were ADA positive (63, 68). The occurrence rates of CRS or CAR-T cell-related neurotoxicity were similar between ADA positive and ADA negative subjects (67, 68). ADA started to be detectable around Day 100 post ciltacabtagene infusion (67). No conclusion was made regarding the effect of ADA on the initial expansion and persistence, efficacy, or safety of ciltacabtagene (63). The absence of impact on efficacy provides a rationale for not performing neutralizing antibody assessments for ciltacabtagene."

3. **Question:** So far, good data on association (seeing lots of camelid+ cells in GI biopsy) but has causation being vigorous established?
   Answer: We have examples of patients who receive cyclosporine, vedolizumab, cyclophosphamide, and/or ruxolitinib and experience rapid relief of symptoms with a concomitant decline and eventual complete absence of Camelid positive cells. We also have examples of patients who get "appropriate" therapy, experience resolution of symptoms, and then go off drug and have rapid return of symptoms. Additionally, we do not see this severe diarrhea with ide-cel (the other FDA approved anti-BCMA CAR) or other FDA approved CARs (to CD19). Those other CARs to cause adverse events due to high levels of cytokines, but they aren't causing this severe diarrhea. So there is something specific about Cilta cel. When we look in the GI tract, we see high levels of cilta cel in the organ that it failing (GI tract). So I think the circumstantial evidence is quite strong. Additionally, there are suspicious somatic variants in SOCS1, SH2B2, and others that are consistent with the model that these T-cells are prone to excessive activation of the JAK/STAT pathway, but certainly more work needs to be done to understand the molecular pathogenesis.

4. **Question:** Is there any urge to validate any IHC methods for evaluating non-Camelid CAR-T, like FMC63 CD19 CAR-T cells?
   Answer: It would be great to have more tools to determine if infiltrates are derived from CART cells. One tool is in situ hybridization to the woodchuck hepatitis

posttranscriptional regulatory element (WPRE) that is common in many of the lentiviral vectors used for CART cells. See: Wright JH, Huang LY, Weaver S, et al. Detection of engineered T cells in FFPE tissue by multiplex in situ hybridization and immunohistochemistry. *J Immunol Methods*. 2021;492:112955.

5. **Question:** Is there role for counting using digital image analysis?
   Answer: I don't see a need for digital image analysis in this situation at the moment. I don't think there are enough cases to establish an very precise cutoff yet. But certainly if one has access to DIA that works it could be used.

6. **Question:** Are there recurrent gene mutations, particularly those seen in T cell neoplasia, in these LPDs?
   Answer: The case reports have found somatic variants in SOCS1 and SH2B3 that may be playing a role in making these T-cells more prone to excessive/persistent activation but the molecular pathogenesis of this phenomenon is not yet well understood.

7. **Question:** In these patients with IEC-EC with clonal T-cells, are these T-cell clone existed in the patient's T-cells collected for CART?
   Answer: Yes, in one case, a pre-existing SH2B3-mutated clone was detected in 0.4% of PBMCs before CAR T-cell manufacture and this same variant was detected at 26% allele frequency in the duodenum on day 144 post Cilta-cel infusion. This supports a model in which T-cells with a pre-existing genetic predisposition receive additional "hits" (either somatic mutations, integration leading to dysregulation of relevant genes, signaling through the CAR, or a combination of these possibilities) that then lead to IEC-EC/LPD. See Figure 2 in: Hosoya H, Bastidas Torres AN, Fernandez-Pol S, et al. Long-term follow-up of gastrointestinal CAR T-cell lymphoma: homing, clonal expansion, and response to cyclosporine. Blood. 2026;147(11):1191-1198. doi:10.1182/blood.2025031423