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by Shantoi Williams

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Steroid-refractory ICANS after CAR T-cell therapy: the case for prospective evidence. Comment on: "Relapsing, steroid-refractory ICANS after CAR T-cell therapy: diagnostic work-up and response to delayed repeated intrathecal chemotherapy"

Shantoi Williams, MD
Montefiore St Luke's Cornwall Hospital
Correspondence: Shantoi Williams, shantowill@montefioreslc.org
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The recent report by van Nijendaal et al. describes near-complete neurological recovery in a patient with relapsing, steroid-refractory immune effector cell-associated neurotoxicity syndrome (ICANS) who received two delayed administrations of intrathecal chemotherapy, the first 45 days after CAR T-cell infusion.[1] It adds to a small evidence base on a problem of growing relevance. Chimeric antigen receptor T-cell (CAR-T) therapy is now available across B-cell lymphomas, leukemias and multiple myeloma, and ICANS remains one of its most serious complications, with pooled incidences of approximately 27% for all grades and 10.5% for high grades.[2] Corticosteroids are the backbone of first-line management,[3] but a subset of patients become steroid-refractory, with attendant morbidity and mortality.[4] Because high cumulative corticosteroid exposure has itself been associated with inferior CAR-T outcomes,[5] effective options after steroid failure matter for both neurological and oncological reasons. Yet current guidance offers little to direct salvage therapy, and the available evidence consists of small retrospective series and case reports.[6-9]

The largest retrospective series of a single salvage agent is that of Gazeau et al., who analyzed 43 patients across nine centers in whom anakinra was initiated primarily for refractory ICANS (n=40) or cytokine release syndrome (n=3); doses up to 12 mg/kg/day were reported to be safe.[6] The primary objective was safety, however, and the study was uncontrolled, with heterogeneous products and dosing, so it cannot establish efficacy in steroid-refractory ICANS. For intrathecal therapy, Zurko et al. reported a single-center experience in which seven of 15 patients with grade ≥3 ICANS received early intrathecal hydrocortisone, with chemotherapy added in four; ICANS resolved in all seven, and estimated one-year progression-free survival was 57.1%, compared with 18.8% among the eight patients who did not receive early intrathecal therapy (0% in those with steroid-refractory ICANS).[7] Bashey et al. described 12 patients treated with intrathecal chemotherapy, with resolution of ICANS in 11.[8] These studies, together with earlier case-level reports,[9] are small, retrospective and heterogeneous in CAR-T product, ICANS grading, intrathecal agents and timing. The case of van Nijendaal et al. suggests that intrathecal treatment may still be effective well after the window previously considered relevant, but a single case cannot define optimal agents, dosing, timing or predictive biomarkers.[1]

As a result, the choice of salvage agent, dose and time of escalation is made largely on institutional experience. Publication bias toward favorable outcomes compounds the problem, and the risks of intrathecal chemotherapy in this setting, including lumbar puncture in patients who are often cytopenic or coagulopathic, chemotherapy-related neurotoxicity, and possible effects on CAR-T function, are poorly characterized. The number of patients exposed will continue to rise as indications expand and new constructs enter clinical use.

We therefore propose two complementary steps. First, a prospective international registry should capture, using standardized ASTCT grading,[10] the clinical presentation, definition of steroid refractoriness, salvage agent, dose, timing and neurological trajectory of every case of steroid-refractory ICANS. Second, an adaptive platform trial, ideally embedded in that registry to accommodate the rarity and urgency of the condition, should compare leading salvage strategies, including anakinra and intrathecal therapy. Primary endpoints should reflect neurological recovery, for example time to ICANS grade ≤1 and ICE score or functional status at day 28, with steroid exposure, safety, CAR-T response and survival as key secondary endpoints. In parallel, the ASTCT, EHA and EBMT could build on existing guidance[3] to define steroid-refractory ICANS and provide consensus recommendations on escalation timing and patient selection.

Case reports such as that of van Nijendaal et al. are valuable for generating hypotheses. Turning them into evidence that can guide care at the bedside will require prospective, collaborative studies.

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