Chimeric Antigen Receptor T-cell Therapy: Imaging Response Criteria and Relation to Progression-free and Overall Survival

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Chimeric antigen receptor T-cell therapy (CART) uses patient-derived tumor antigen-directed T cells for targeted elimination of cancer cells. The most common form applies modified T cells expressing a chimeric antigen receptor specific for the CD19 antigen to treat relapsed or refractory (rr) lymphoma1 and leukemia, leading to high rates of durable responses. CART has significantly improved progression-free survival (PFS) and overall survival (OS). Imaging-based response assessment for determination of PFS has most frequently relied on positron emission tomography-computed tomography (PET/CT). The current and ongoing phase III trials are mostly based on the Lugano criteria from 2014.3,4 Earlier trials have relied on Cheson criteria as published in 2007.5 In recent years, novel lymphoma imaging response criteria have been proposed, among them the response evaluation criteria in lymphoma (RECIL),6 and lymphoma response to immunomodulatory therapy criteria (LYRIC).7 The scientific literature on structured comparisons of these imaging response criteria is scarce for conventional lymphoma treatments and only 2 studies indicate concordance of RECIL and Lugano criteria in previously untreated lymphoma.8,9 As there are no reports on the prognostic value for lymphoma patients treated with CART, we aimed to assess the different imaging response criteria, their impact on PFS, and their relation to OS.

The study population was based on a prospective registry of all consecutive patients who were treated at the Comprehensive Cancer Center Munich-Ludwig-Maximilian University Munich (CCCMLMU) with commercialized CD19-specific CART products. We included patients with refractory or relapsed lymphoma (DLBCL, FL, and MCL), any measurable disease on imaging according to Lugano criteria,1 and available (PET/CT) imaging studies at baseline and at least 2 follow-up timepoints (FU1 around 30 days and FU2 around 90 days). All medical records and imaging studies were reviewed with the approval of the LMU Munich Institutional Review Board (Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München, Project Number 19-817) and informed patient consent. Patients received lymphodepletion with fludarabine and cyclophosphamide according to the approved study protocol (CCCMLMU) with commercialized CD19-specific CART products. We included patients with refractory or relapsed lymphoma (DLBCL, FL, and MCL), any measurable disease on imaging according to Lugano criteria,1 and available (PET/CT) imaging studies at baseline and at least 2 follow-up timepoints (FU1 around 30 days and FU2 around 90 days). All medical records and imaging studies were reviewed with the approval of the LMU Munich Institutional Review Board (Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München, Project Number 19-817) and informed patient consent. Patients received lymphodepletion with fludarabine and cyclophosphamide according to the approved study protocol (CCCMLMU) with commercialized CD19-specific CART products.
The evaluation of overall response and response patterns, including the impact of pseudoprogression associated with CAR T-cell therapy, has not yet been studied in detail. Some studies described pseudoprogression after CART analogous to solid tumors under immunotherapy. To face the challenge of pseudoprogression, LYRIC introduced the category of IR, with 3 subcategories: IR1, increase in overall tumor burden within the first 12 weeks of therapy, without clinical deterioration; IR2, appearance of new lesions, or growth of one or more existing lesions ≥50% at any time during treatment in the absence of overall progression; IR3, increase in FDG uptake of one or more lesions without a concomitant increase in lesion size or number. LYRIC encouraged biopsy for IR1 and IR2 and advised to evaluate these intermediate features by follow-up in all cases after 12 weeks. In contrast to LYRIC, Lugano or RECIL do not provide recommendations for lesion follow-up. Therefore, patients with assigned PD solely based on newly appearing lesions should be further investigated with regard to clinical benefit and may represent a new response category. Novel imaging endpoints and response criteria in lymphoma will likely evolve from selected lesion-based assessments to whole tumor burden quantification. In the first-line setting, the recently published International Metabolic Prognostic Index (IMPI) additionally integrates metabolic tumor volume and has outperformed the conventional IPI in estimating outcome of DLBCL patients.

We investigated overall response by Lugano criteria, Cheson criteria, RECIL, and LYRIC. While the ORR was comparable between the different criteria, we found striking differences between the SD and PD response categories and thus discrepancies in the surrogate endpoint PFS. Response assessment by LYRIC exhibited superior association between PFS and OS. The response assessment method must therefore be considered when interpreting the impact of imaging endpoints on outcomes in clinical trials. Our study has limitations which need to be considered when interpreting the results. First, this is a single-center study with a limited number of subjects. Second, there were a few patients that were missed to follow up or had no measurable disease. Considering the heterogeneity, our results argue for standardization and harmonization across centers.

**AUTHOR CONTRIBUTIONS**

MW and WGK conceived and design the study; VLB, VB, KR, MR, MU, and CS collected the data; MW, VLB, VB, KR, and WGK analyzed and interpreted the data; and MW and WGK drafted the manuscript; and KR, FJD, PB, JR, MvB-B, and MS revised the manuscript.

**DISCLOSURES**

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