CAR T-cell therapy for triple-class exposed relapsed/refractory multiple myeloma

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Received: March 10, 2023.
Accepted: March 23, 2023.
Early view: April 6, 2023.

https://doi.org/10.3324/haematol.2022.282587

The treatment landscape for multiple myeloma (MM) has expanded progressively during the past two decades to include multiple proteasome inhibitors (PI), immunomodulators (IMiD), and monoclonal antibodies (MoAb). These agents are the pillars of modern MM therapy for both newly-diagnosed patients and those with relapsed/refractory disease. When given simultaneously, these agents allowed enhanced rates and depth of durable responses to be achieved, even in more advanced phases of the disease. Not surprisingly, these benefits led to significant improvements in progression-free survival (PFS) and overall survival (OS).[1] Nevertheless, most patients eventually relapse and become progressively refractory to the main classes of agents during successive lines of therapy. For many years, no standard of care treatment was established in real-world clinical practice for patients exposed or refractory to at least an IMiD, a PI and a MoAb, referred to as triple-class exposed or triple-class refractory, who are candidates to receive T-cell redirecting therapies. Results from the retrospective MAMMOTH study demonstrated the poor outcomes for these therapeutically challenging patients, highlighting the need for more effective treatments with novel mechanisms of action.[2] CAR T-cell therapies are likely to provide significant benefits in this setting, based on deep and durable disease control as shown in exploratory phase II clinical trials.[3,4] However, the absence of a control arm in the KarMMa and CARTITUDE-1 studies, which led to approval of idecabtagene vicleucel (ide-cel)[3] and cilcabtagene autoleucel (cilta-cel),[4] respectively, by regulatory agencies, raised the need for indirect evidence on the relative effectiveness of these novel therapies compared with real-life treatments. For this purpose, indirect treatment comparisons are possible by creating an external control arm from either real-world or clinical trial data sources. To avoid clinical outcome estimates that are biased by imbalances in baseline prognostic characteristics of non-randomized cohorts of patients, statistical methods that account for such confounding biases should be applied.

In the current issue of *Haematologica*, Mateos *et al.*[5] report the results of a study aimed at retrospectively comparing the effectiveness of cilta-cel in the context of the single-arm of the CARTITUDE-1 study with real-world data extracted from the LocoMMotion study,[6] the first prospective, non-interventional, real-life study of triple-class exposed MM patients. Overall, 113 patients were enrolled in CARTITUDE-1, and 97 of these were infused with cilta-cel after a mean of 52 days from the date of apheresis, while the remaining 16 patients discontinued the study after apheresis. The LocoMMotion study involved a total of 248 patients from European countries and the US who were triple-class exposed, the majority of them also triple-class refractory, after a median of four prior lines of therapy. Based on physicians' choice, these patients received 92 treatments, each of them unique to the individual patient, a finding which reflects the lack of a standard of care therapy in this setting.

Matched-adjusted comparisons of individual patient data from CARTITUDE-1 and LocoMMotion studies were performed using inverse probability weighting methods to estimate the average treatment effect in the respective cohorts of patients. For the purposes of the study, two analyses were performed. The first of these involved the so-called infused/aligned cohorts and was aimed at comparing individual patient data from the set of 97 patients who were treated with cilta-cel with the aligned cohort of 170 patients from LocoMMotion who were progression-free and alive 52 days after start of treatment. This time period corresponded to the average time during which patients were required to be progression-free and alive in order to receive cilta-cel infusion in CARTITUDE-1, and was chosen to align the LocoMMotion cohort with the set of patients from CARTITUDE-1. The observed rates of response, including complete response or higher, at least very good partial response and partial response, were significantly higher in the cilta-cel-treated group (82.5%, 94.8%, and 97.9%, respectively) compared to the real-world treated group (0.6%, 17.6%, and 42.9%, respectively). Adjusted

comparisons between the two cohorts showed that patients treated with cilta-cel were 5.7 times (95% CI: 3.25-8.08; *P*<0.0001) more likely to achieve at least a very good partial response than patients treated in the real-world clinical practice. The observed median PFS for this latter group was 4.3 months, while it was not reached in the cilta-cel-treated group. Adjusted and unadjusted hazard ratios (HR) for the set of patients who received CAR T-cell therapy compared to conventionally treated patients in real-world clinical practice were 0.15 (95% CI: 0.08-0.29; *P*<0.0001) and 0.19 (95% CI: 0.12-0.29; *P*<0.0001), respectively. Following adjusted comparison for OS, a reduced risk of death by 80% (HR 0.20, 95% CI: 0.09-0.41; *P*<0.0001) favored patients treated with cilta-cel *versus* the real-world treated group (who had an observed median OS of 11.3 months), a finding which supported the results of the unadjusted comparison between these groups. The second analysis included the overall cohorts of 113 and 248 patients enrolled on the CARTITUDE-1 and LocoMMotion studies, respectively, and substantially confirmed the results reported above. Overall, the magnitude of incremental improvements over time in patients' quality of life measured by means of two different questionnaires was considerably higher for those who were alive and progression-free in the cilta-cel group *versus* patients in the real-world group. In particular, the difference in improvement *versus* baseline favoring CAR T-cell therapy was 13.4 at week 52 (*P*=0.0081) and increased to up to 30.8 (*P*<0.0001) when the analysis included death as an additional factor regarding patients' health status. Patients infused with cilta-cel experienced more adverse events compared to the LocoMMotion study, although in this latter group the incidence was likely to be underestimated.[6]

The study by Mateos *et al.* supports the meaningful improvements offered by cilta-cel compared to physicians' choice of therapy in triple-class exposed patients with relapsed/refractory MM. Results are consistent with similar analyses of cilta-cel *versus* other external cohorts[7-9] and contribute to the growing body of evidence highlighting the potential of CAR T-cell therapy as a novel treatment strategy to address the high unmet need of this hard-to-treat set of patients. Although the prospective design of the LocoMMotion study and its alignment with CARTITUDE-1 for most of the eligibility criteria and clinical outcome measures allowed a robust comparison of cilta-cel *versus* conventional therapies, the potential for confounding bias related to missing or unobserved patients' characteristics cannot be ruled out. Data on cytogenetics were not available in approximately one-third of patients enrolled into the LocoMMotion study.[6] This finding precluded the possibility of making any adjustment for cytogenetic risk in the main analysis and represents a limitation of the study. In addition, two other prognostic variables of interest (i.e., prior history of stem cell transplantation and race) were not considered in the base case scenario since their inclusion had a negative impact on the balance between study populations. Another study limitation is represented by the limited number of patients treated with belantamab mafodotin and selinexor, which are currently approved for the management of triple-class refractory and penta-refractory MM (i.e., refractory to the two ImiD lenalidomide and pomalidomide, the two PI bortezomib and carfilzomib, and the anti-CD38 MoAb daratumumab). Although this finding did not allow any evaluation of the relative effectiveness of cilta-cel *versus* these newer agents, results from such a comparison were reported elsewhere.[9] CARTITUDE-4, a phase III randomized study comparing cilta-cel with standard of care regimens for lenalidomide-refractory patients after 1-3 prior lines of treatment including a PI and an IMiD, will more precisely inform clinical decision-making as to the efficacy and safety of cilta-cel in a less heavily pre-treated setting of MM patients.[10]

Disclosures

No conflicts of interest to disclose.

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