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Quality of life and CAR T-cell therapy in children, adolescents, and young adults with haematological malignancies

Remarkable treatment advances have been made over the past two decades in haematological research, making the evaluation of quality of life and of other types of patient-reported outcomes (PROs) crucial to clinical decision making.[1] Development of chimeric antigen receptor (CAR) T-cell therapies for patients with haematological malignancies is a recent example of this outstanding progress, and poses some specific challenges to the assessment of PROs.[2]

In *The Lancet Oncology,* Theodore Laetsch and colleagues[3] assessed quality of life in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia treated with CAR T-cell therapy, a single infusion of tisagenlecleucel.[3] Although efficacy and safety data of tisagenlecleucel were previously documented in the pivotal study,[4] leading to the approval of this therapy by the US Food and Drug Administration and European Medicines Agency, only by reading Laetsch and colleagues' Article[3] can we appreciate how this therapy has affected patients' lives, from their own perspective. The comprehensive quality-of-life analysis[3] is of particular value, as a recent systematic review on studies using CAR T-cell therapies, both in solid and haematological malignancies, has found no full-length published articles (ie, no abstracts) reporting data on patient-reported quality-of-life outcomes.[5]

In Laetsch and colleagues' study,[3] 58 patients with relapsed or refractory B-cell acute lymphoblastic leukaemia aged 8 years or older were eligible for analysis of quality of life, which was evaluated at baseline (before infusion of tisagenlecleucel) and then at day 28 and months 3, 6, 9, and 12, using two validated questionnaires: the Pediatric Quality of Life Inventory (PedsQL) and the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.

Baseline compliance with quality-of-life assessment was good: 50 (86%) of patients completed PedsQL and 48 (83%) completed the EQ-5D visual analogue scale. The level of compliance is notable considering the multicentre and international setting of the study, which included children and young adults with a highly debilitating and potentially life-threatening condition. Indeed, already at the time of study inclusion, the quality-of-life profiles of participants were substantially impaired compared with the general population, and more than 50% of them had undergone at least one haemopoietic stem-cell transplantation.

Laetsch and colleagues[3] found some improvements in quality of life measures as assessed with both questionnaires, albeit not clinically meaningful, as early as day 28. At this very early timepoint, the scale showing the greatest positive change from the PedsQL questionnaire was emotional functioning. Further improvements were increasingly found at subsequent timepoints up to 12 month and, notably, these were also clinically meaningful across several quality-of-life domains, with the largest improvement found for the physical functioning scale of the PedsQL. In additional subgroup analyses, improvements in quality of life from baseline to month 12 were also found for patients who reported a severe grade of cytokine release syndrome or neurotoxicity status, but these improvements

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See **Articles** page 1710

were generally of greater magnitude from month 6.[3] This finding is important because in the original trial[4], cytokine release syndrome and neurological events were major safety concerns, with cytokine release syndrome occurring in 77% of patients and neurotoxicity occurring in 40% of patients.

Preliminary studies of the impact of CAR T-cell therapies on very short-term quality of life of patients with other haematological malignancies were recently presented at major international meetings, broadly providing reassuring results.[6–8] Notably, a prospective comparative analysis on patients receiving CAR T-cell therapy (n=10) versus autologous stem cell transplantation (n=22) or allogeneic stem cell transplantation (n=13) up to 1 month from baseline assessment suggested that patients who received CAR T-cell therapy did not have more significant overall decline in quality of life than those who underwent autologous and allogeneic stem cell transplantation.[6] Specifically, the decline in the physical wellbeing scale was less evident in the group of patients treated with CAR T-cell therapy, and this decline was particularly notable 2 weeks after baseline.[6] However, it is challenging to compare findings across the few preliminary studies in this area because of different research designs, PRO measures used, and haematological populations considered. Standardisation of PRO assessment methodology is important in this challenging area of immunotherapy to rapidly inform patient care.

Although Laetsch and colleagues[3] provided a rationale for the selection of their quality-of-life measures, no information regarding key cancer symptoms can be obtained from these measures. Indeed, the questionnaires used in their study[3] were mainly focused on capturing more general health and psychosocial aspects, thereby limiting a thorough understanding of patient-reported symptom burden. Given the specific toxicity profile of CAR T-cell therapies, evaluation of (patient-reported) symptomatic adverse events is recommended. Various options could be considered in future studies—eg, the inclusion of selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events[9] or from its more recent and currently in development paediatric version,[10] as applicable, depending on patients' age.

It will also be important to investigate long-term quality-of-life outcomes (ie, beyond the 12-month period of observation) in this younger acute lymphoblastic leukaemia population, by including an evaluation of symptoms and cognitive aspects, and possibly to compare findings with long-term quality-of-life data of patients treated with traditional therapies for acute lymphoblastic leukaemia.

In conclusion, the authors should be commended for their efforts to provide the scientific community with unprecedented PROs information on the burden of this CAR T-cell therapy. Despite several open questions, which should be elucidated in further studies, the results reported in their article[3] are highly encouraging and hopefully will stimulate other high-quality research initiatives in this area.

*Fabio Efficace, Marco Vignetti
Italian Group for Adult Hematologic Diseases (GIMEMA), Data Center and Health Outcomes Research Unit, 00161 Rome, Italy (FE, MV)
f.efficace@gimema.it

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