Educational Needs for Physicians

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CAR-T cells are novel therapies associated with promising and potentially curative outcomes in patients with high-risk relapsed disease. In Europe, there are currently three approved products (tisagenlecleucel, axicabtagene ciloleucel, and brexucabtagene autoleucel) for patients with acute lymphoblastic leukaemia, aggressive B-cell lymphoma, and mantle cell lymphoma, although expanded haematologic and non-haematologic indications are expected soon.

Cellular therapy, including CAR-T cells, is a rapidly evolving field in haematology, and treatment is becoming personalized and specific. To ensure optimal decision-making by physicians, adequate education programmes must be available and must be regularly updated. There is a need to identify knowledge gaps and barriers to address these issues with continuous medical education. Adequate education increases the competence and performance of physicians and improves the quality of decision-making, ultimately resulting in the optimization of patient management. The importance of education is also reflected in the JACIE accreditation scheme, the major objective of which is to promote quality medical and laboratory practice in cellular therapy by offering accreditation based on internationally recognized standards. The relevant standards in this scheme require that clinical, collection, and processing facility staff participate in continuous education activities (JACIE 2021). However, there is also a need to educate the wider community (people who do not

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N. Kröger et al. (eds.), *The EBMT/EHA CAR-T Cell Handbook*,
https://doi.org/10.1007/978-3-030-94353-0_39

work at JACIE accredited sites) to ensure sufficient knowledge to recognize the role of CAR-T therapy, identify suitable patients and understand the process for timely referral to treatment centres. There is an inevitable delay between referral, cell collection, and delivery of the CAR-T products, and physicians must be aware of this process and take steps to manage their patients, who are at high risk of rapid disease progression and may require bridging therapy, ideally in close collaboration with the CAR-T treatment centre. Therefore, referring physicians must be educated to understand the patient selection process, T cell collection process, and the processing and conditioning therapy to fully understand the path that their patients will travel and the time frames involved in delivering these complex treatments.

CAR-T cell therapies are associated with remarkable therapeutic response rates but also with unique and potentially lethal complications that require specific educational updates. Cytokine-release syndrome (CRS) and neurotoxicity are the most frequent complications after CAR-T cell therapies. These complications can occur concomitantly and may have a very rapid onset, with a spectrum of symptoms that range from mild to life threatening. In addition, CRS onset is often indistinguishable from infection, which, in the setting of neutropenia, makes the management of these complex patients even more challenging (Hayden et al. 2021). Haematologic toxicity, most often seen as a complication of lymphodepleting induction therapy, is frequent after CAR-T cell infusion, but the pattern, duration, and outcome are not well described. Learning to monitor and adequately treat persistent cytopenias is necessary for adequate management of these patients. Learning to define the optimal timing for ICU referral is also critical because any delay in ICU admission can compromise patient outcomes. In addition, the unique toxicity profile of CAR-T cell therapies makes incorporation of real-life data, including that from the patients' perspective, essential, and initial data suggest that patient-reported toxicities and mental health concerns are common throughout all stages of survivorship (Barata et al. 2021; Hoogland et al. 2021). From the moment that a patient is identified as a CAR-T candidate, education and supportive care of patients undergoing CAR-T therapy is crucial to improve the knowledge and experience of the patients and their families. To address these issues, a trained multidisciplinary team, including haematologists, oncologists, intensivists, neurologists, pharmacists, psychologists, and nurses, must work together from the time of potential patient identification to the time of treatment and discharge, and their roles are crucial at different stages in the CAR-T cell process.

Large registry studies with high-quality data may provide the basis of knowledge for CAR-T cell therapies and open the door to the necessary specific subpopulation investigations. To ensure continuous evaluation of the efficacy and safety of commercially available CAR-T cells, the EMA endorsed the use of the EBMT registry for collection of 15-year follow-up data of treated patients (EMA 2019). Likewise, follow-up data of patients receiving academic and other pharmaceutical-sponsored CAR-T cell therapies are also expected to be reported to the EBMT registry. Therefore, the real-world data contained in the EBMT registry will likely be a major source of knowledge to improve the use of CAR-T cell therapies and to understand the short-term and long-term patient toxicities and outcomes. This will also allow us

to gain insights into potential biomarkers and the patient and disease characteristics that might impact the efficacy of CAR-T-treatment, opening the path to more effective selection and stratification of patients.

Ongoing investigations of CAR-T cell therapies are seeking to elucidate the mechanisms of resistance, immune escape, and relapse so that the current barriers can be overcome and treatment efficacy can be improved. Research is also focused on access to "off-the-shelf" allogeneic CAR-T products, simplifying the manufacturing process and mitigating side effects, among other aims. Thus, the complexity and rapid changes in the field of cellular therapies demands wide collaboration to maintain up-to-date education on the entire pathway from collection to the manufacturer and back to the clinical unit. GoCART, a multistakeholder coalition launched by EBMT and EHA, offers a platform to provide the required diversified and topic-specific education on CAR-T cell therapies. Likewise, the annual EBMT/EHA European CAR-T cell meeting provides specific continuous medical education in this complex field. In addition, educational online updates are provided on the EBMT and EHA e-learning platforms (https://www.ebmt.org/education/e--learning, https://ehacampus.ehaweb.org) with specific webinars and e-learning courses focused not only on CAR-T cells but also on other evolving immunotherapy treatments that may impact the pathway towards CAR-T cell treatment. There is still much to learn, and this rapidly evolving field requires rapid and constant educational updates.

Key Points

- Continuous medical education should fill unavoidable knowledge gaps in a rapidly evolving field.
- Big data registry studies, multistakeholder coalitions, and multidisciplinary educational meetings provide regular updates on the entire CAR-T cell therapy process.
- Updates on specific topics and the latest scientific developments are also required to provide individualized high-quality patient management.
- e-learning platforms and CAR-T cell meetings provide adequate and specific updates in this complex field, but there is also a need to educate the wider medical community, who refer patients to treatment centres.
- Continuous medical education is necessary, especially because this field is rapidly evolving.

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