

Workshop on the Current Status of Cell and Gene Therapies: The CAR-T Cell Model Workshop Report (TSH-CGT SSC Activity)

The increasing success of cellular therapies in clinical applications has facilitated the qualitative and quantitative advancement of preclinical and clinical research in this field. The use of T cells for therapeutic purposes in patients with relapsed or refractory cancer is defined as adoptive cellular therapy. The most significant advanced T-cell therapy product in this field is chimeric antigen receptor-expressing T-cell (CAR-T cell) therapy, which, through genetic modification, targets tumor antigens to kill tumor cells. In particular, the demonstration of the efficacy of CD19 CAR-T cell therapies in B-cell-derived hematological cancers through clinical trials has led to the approval of these products for clinical use by the U.S. Food and Drug Administration and the European Medicines Agency. Consequently, with an increase in biotechnology companies investing in this field, particularly in the United States and other developed countries, industry-academia collaborations have been established. This has led to a growing number of CAR-T cell products, which are evaluated under different regulatory statuses (i.e., commercial CAR-T cell products or academic CAR-T cell products approved for limited clinical use under special authorization). The number of CAR-T cell products has been steadily increasing. It is projected that CAR-T therapies, which are included in treatment options in international guidelines, will reach the highest market share (~50%) in the oncology drug market by 2026, particularly for the treatment of pediatric acute lymphoblastic leukemia and adult B-cell lymphoma.

While there are ongoing efforts in Türkiye regarding the development, production, and clinical application of advanced cellular therapies, which must be delivered to patients as quickly as possible during a critical life-or-death window, these efforts do not yet meet the required level. It is inevitable that commercial CAR-T cell products, marketed at high costs by international biotechnology companies, will be made available to our patients in Türkiye. The economic burden that these innovative treatments will place on healthcare expenditures will be significant. Furthermore, legal regulations and oversight regarding CAR-T use have not yet been established. It is imperative that our clinical trials begin as soon as possible, in accordance with comprehensive national ethical guidelines and regulations, through the formation of an academic consensus to meet the needs of patients in this country.

Organized by the Turkish Hematology Association's Cell and Gene Therapies Scientific Subcommittee (TSH-CGT SSC), the purpose of this workshop was to assess the current status of advanced cell and gene therapies, particularly CAR-T cell therapies, in our country and to develop a production and application model suitable for our national context. The goal was to determine the current status regarding research infrastructure, resources, trained personnel, existing regulations, and clinical practices in this field and to clarify the challenges and potential solutions. This meeting was the first in a series of workshops aimed at fostering constructive and productive collaborations between basic scientists and clinicians, establishing national production/clinical application teams, and developing the Türkiye CAR-T Model with the contributions of health authorities.

Preparations for the workshop began in December 2022. A survey form was sent to all members via the THD forum platform in April 2023 to assess the current status of CAR-T cell production and use (Appendix 1: Survey). Based on the responses to the survey, insights were gained regarding the proportion of patients in our country who may require CAR-T cell therapy and the current infrastructure conditions. On June 3, 2023, a workshop titled "Current Status Workshop on Cell and Gene Therapies: The CAR-T Cell Model" (Appendix 2: Workshop Program) was held in Ankara as part of the Turkish Hematology Association's TSH-CGT SSC Activity, with 64 participants in attendance. Participants primarily came from hematology departments, as well as genetics, biochemistry, biophysics, pharmacology, physiology, medical biology, biomedical sciences, and immunology departments. Additionally, members of clinical research ethics committees, quality unit coordinators, and representatives from the Turkish Medicines and Medical Devices Agency (TİTCK), Türkiye Health Institutes (TÜSEB), and the Directorate of Organ Transplantation and Dialysis Services under the General Directorate of Health Services (SHGM) attended.

The workshop program began with a presentation of the survey results. According to the survey, 98% of hematologists indicated that they would like to use CAR-T cell therapy for patients with B-cell hematologic cancers who have experienced treatment failure, provided it is available; 60% stated that they could use this treatment option as a "bridge therapy" to stem cell transplantation. While most participants indicated that the necessary prerequisites for administering CAR-T cell therapy could be met in their clinics, only a limited number of centers reported having the necessary conditions for CAR-T cell production. These survey results indicate a high level of awareness within the field of hematology regarding CAR-T cell production and clinical use in Türkiye, confirming that there is a need for this treatment method and that demand would grow rapidly and the therapy would be adopted for our patients if it becomes accessible.

The meeting was organized according to four main headings, with experts in each field outlining the key points of their respective topics:

- 1. Current Status of CAR-T Cell Therapies:** Following the first presentation, which provided a detailed explanation of the terminology and scope of advanced therapeutic products, the clinical use of CAR-T cell therapies for adult and pediatric patients was evaluated in light of international data.
- 2. CAR-T Cell R&D and Manufacturing Process:** The critical steps involved in transitioning CAR-T cells from the laboratory to the clinic were examined. The importance of quality control steps necessary for the use of new cellular products in clinical trials, the resolution of issues identified during the process, and the ongoing nature of R&D efforts for product development were

emphasized. The topics of viral vectors and T-cell engineering, which are of great importance for the development of CAR-T cells that meet international standards and are safe, were then examined in detail. As part of a research project in Türkiye funded by TÜBİTAK, the process of developing a viral vector carrying the CAR-19 construct for clinical use was presented in detail by the principal investigator. The challenges associated with establishing, licensing, operating, and ensuring the sustainability of good manufacturing practice (GMP) laboratories, which are necessary for the clinical production of advanced therapeutic products, under our country's conditions were highlighted. It was suggested that, rather than establishing new GMP laboratories, which are extremely costly to set up and operate and require an experienced workforce in the field of cell and gene therapies, existing licensed GMP laboratories at selected centers could be utilized. Furthermore, it was emphasized that each GMP laboratory can work on the products for which it has received a license, thereby enabling the development of suitable models for the production of CAR-T cell therapies. In this section of the meeting, historical errors and delays encountered during the vector development process were also addressed, and discussions focused on the necessary path forward. Attention was drawn to the current state of CAR-T cell technology and its evolving direction, with an emphasis on closely monitoring developments to ensure its prompt implementation in our country. Although these therapies may initially require very large budgets, it was emphasized that they could contribute to patient health and the state/healthcare service economy in the long term. The importance of evaluating pharmacoeconomic assessments not in the short term but by projecting them over a 5- to 10-year period was discussed.

3. **Regulatory Steps for Advanced Therapy Medicinal Products (ATMPs): Scientific and Legal Regulations from Production to the Clinic:** Definitions of ATMPs, as well as ethical and administrative regulations and guidelines in Türkiye and around the world, were discussed. Recent regulations regarding quality management in cellular therapies, particularly those such as the FACT-JACIE standards, were examined, along with an assessment of the strengths and weaknesses in the statutes and regulations published in 2005, 2018, and as recently as this year [2023]. The ATMP regulation published on May 27, 2023, was reviewed article by article and interpreted, with the highlighting of inconsistencies and contradictory statements compared to previous regulations. The importance of using common terminology and achieving consensus on the definition of concepts was emphasized. Additionally, the importance of cellular therapy practitioners having sufficient knowledge and resources to evaluate the quality of the products they use was emphasized.
4. **Planning and Managing Clinical Trials Related to Cell and Gene Therapies, and Examples of Research in this Field from Our Country:** Current regulations in Türkiye regarding this subject were discussed in detail together with the critical role of developing highly efficient viral vectors in clinical outcomes based on our country's very limited experience with CAR-T-cell therapy; the lack of sufficient funding for R&D and clinical research; the necessity of establishing teams composed of qualified researchers and clinicians; deficiencies and errors in the planning, conduct, and oversight of clinical trials; and challenges encountered during patient follow-up. The need for regulations regarding treatments conducted under the guise of clinical trials or studies, where outcomes are unpredictable, and the ability to administer such treatments without charging patients was also discussed.

Finally, the panel addressed the reasons for the delays in R&D and clinical research/applications of advanced cell and gene therapies in our country, as well as current challenges and potential solutions.

The participants' consensus was that Türkiye possesses sufficient laboratory and clinical infrastructure, competent researchers and clinicians in the field, fundamental legal/bureaucratic regulations, and ethics committees. It was noted that by addressing deficiencies in each of these areas through new regulations, global standards could be achieved. It was observed that all participants supported collaborative initiatives regarding the development, production, and clinical use of CAR-T cells, and they were in agreement on the need to develop a production and application model suitable for Turkish conditions.

The workshop results can be summarized as follows:

1. CAR-T cell therapy is not yet a fully developed treatment model; there are still many areas in this field that are open to further development and refinement. Through the collaborative efforts of scientists from fields such as genetics, biology, pharmacology, biotechnology, and engineering, as well as from medical disciplines including immunology, hematology, and oncology, Türkiye will be able to keep pace with the rapid change and transformation in this field. These collaborations and joint research areas will provide opportunities for the recruitment, training, and retention of human resources in this field.
2. CAR-T cell therapy for patients with relapsed and refractory B-cell acute lymphoblastic leukemia, multiple myeloma, and lymphoma has been included in treatment guidelines in the United States and Europe. Türkiye must immediately initiate research, development, production, and clinical applications related to advanced cell and gene therapies; make these treatments available to patients; and incorporate them into national treatment guidelines.
3. There are a sufficient number of GMP-compliant laboratories with the necessary equipment in academic institutions in Türkiye capable of producing CAR-T cells.
4. With the identification of all existing infrastructure and resources in our country, the supporting of collaborations among experienced researchers and clinical teams in this field, and the ensuring of sufficient funding (TÜBİTAK-TÜSEB-industry and industrial partnerships) for R&D and clinical trials, planning clinical trials from the R&D phase onward, obtaining approvals,

monitoring/auditing results, and updating legal regulations are crucial for making rapid progress in this field.

5. Industrial/commercial CAR-T cell products have not yet been introduced in Türkiye due to reimbursement issues and health regulations regarding advanced therapy cellular products. Industrial/commercial CAR-T cell therapy is a high-cost treatment. Academic CAR-T therapies, however, are the most suitable model for our country due to their relatively low cost. The structural and legal frameworks necessary for the production and application of academic CAR-T therapies must be accelerated. This will help alleviate the financial burden that innovative therapies place on the healthcare economy.
6. Considering the academic CAR-T models preferred in countries such as Spain, Israel, China, and the Netherlands, our country's current research infrastructure and skilled workforce are sufficient for the production of CAR-T therapies with Turkish patents.

TSH-CGT SSC's post-workshop objectives were identified as follows:

1. Submission of the workshop report to the relevant institutions, including the General Directorate of Health Services (SHGM), the Turkish Medicines and Medical Devices Agency (TİTCK), the Scientific and Technological Research Council of Türkiye (TÜBİTAK), and the Turkish Health Institutes Presidency (TÜSEB).
2. Organizing the second workshop in the series on the topic of "Options for Rapid CAR-T Production (Semi-Automated and Automated Systems) and the Future," with the participation of industry representatives and all relevant disciplines and stakeholder authorities.