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CAR T-Cell Therapies: Pharmacovigilance Challenges

Cases of secondary tumours have been reported as a possible adverse reaction to the treatment of certain blood cancers with CAR T-cells. A recent analysis of the cases reported to the Paul-Ehrlich-Institut highlights the challenges in the assessment of these newly diagnosed T-cell diseases. The result: in order to better assess these rare but serious cases and identify possible risk factors, CAR T-cell-specific assessment criteria should be defined in pharmacovigilance activities and specific molecular test methods should be established. These steps will further increase patient safety.

CAR T-cell therapies have established themselves as a frequently very successful and overall promising treatment option for various blood cancers for which no other effective therapies are available. However, since the introduction of this therapy, isolated cases of secondary, i.e. new, cancers have been reported, which are caused by T cells and can be a potential adverse reaction of the treatment.

Lack of Data for Causality Assessment of T-Cell Cancers

A group of Paul-Ehrlich-Institut experts from the Medicinal Products Safety Division; the Haematology, Cell and Gene Therapy Division; and the Molecular Biotechnology and Gene Therapy Research Group worked with the Internal Medicine Division of the University Hospital Cologne to analyse the causality assessment process for T-cell-caused cancers reported to the Paul-Ehrlich-Institut in connection with CAR T-cell therapies.

As the analysis shows, the detailed information needed for a well-founded causality assessment of the observed secondary cancers is often lacking. Molecular tests on tumour samples in particular are of great importance according to the team of experts. This allows for an assessment of the gene shuttle itself, the vector integration sites, i.e. the sites in the genome of the cells where the new genetic information is incorporated, and their effects. These tests require the availability of suitable tumour samples and should be considered after diagnosis to enable accurate assessments.

Studying these cases also highlights the complexity of medicinal product safety and the challenge of assessing potential risks of these advanced therapeutics. The criteria established for the causality assessment of suspected adverse drug reactions according to the WHO-Uppsala Monitoring Center (WHO-UMC) do not take into account the characteristic features of gene therapy products (such as onetime treatment and permanent vector integration).

The authors of the study therefore propose the use of modified criteria. They emphasise that it is necessary to establish a uniform approach for causality assessment in order to be able to correctly assess secondary T-cell cancers as a potential side effect and to use laboratory methods that can detect vector integration and screen for oncogenic effects. Such actions are the only way to achieve a deeper understanding of the risk factors and a better assessment of the safety of CAR-T therapies.

Background – CAR T-Cell Therapy

CAR-T cell therapy involves providing the patient's own immune cells (T cells) with a genetically modified (chimeric) antigen receptor (CAR) outside the body (ex vivo). This process is done with the help of gene shuttles (viral vectors), which transfer the genetic information for the CAR into the genome of the T cells. Once altered in this way, the T cells can recognise and fight cancer cells. They are then returned into the patients' blood.

Strict monitoring of CAR T-cell therapies also continues post-authorisation. The marketing authorisation holders of the relevant medicinal products are obliged to regularly submit interim results from the required long-term safety and efficacy studies as well as updated safety reports (Periodic Safety Update Reports, PSURs) to the Pharmacovigilance Risk Assessment Committee (PRAC).

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