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Journal of Organoid & Bioscience

Perspective

Will Black Box Warning Affect Development of CAR-T Therapy

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[1]Macera Therapeutics

Cell therapy has emerged as an approved treatment and has saved many patients. As a living therapy, it serves as a role model for advancements in biology, especially in combating cancer to some extent. Despite the progress in cell therapy, one of the biggest issues on the regulatory side is that the FDA now requires a black box warning for the six cell therapies currently on the market. This announcement was made on January 22nd 2024, mandating producers to remind users about the risk of developing lymphoma. To date, all companies have put the black box warning in their product sheet.

After the announcement, there was a rapid change in the stock market for related companies. However, based on our analysis, there is no need to overreact to such regulatory changes.

1. Many popular drugs have black box warning

Many approved drugs, including some blockbusters, have black box warnings. Examples include JAK inhibitors, GLP-1 inhibitors, and TNF-alpha antibodies. Having a black box warning does not necessarily mean the drug's sales will decline. A good example is Humira, which had a black box warning but still reached annual sales of $20 billion, remaining a top seller for many years.

Another example is the ADC drug DS8201, which gained significant attention for its effectiveness against breast cancer ,especially for Her2 low expression patient. This drug had sales over $1 billion in 2023, despite having a black box warning on interstitial lung disease and embryo-fetal toxicity.

GLP-1 drugs, known for their significant effects on weight reduction, are also very popular now. The market for GLP-1 drugs are over $20 billion, while They also carry a black box warning for thyroid cancer, based on rodent studies.

2. Black box warning as a risk notification

In U.S. law, risk disclosure is crucial. Therefore, it is the duty of the FDA and biopharma companies to list all related risks; otherwise, they may face lawsuits and substantial compensation claims. Hence, the

black box warning is a way to protect both the FDA and biopharma companies. Clinicians are familiar with this practice and will not overreact.

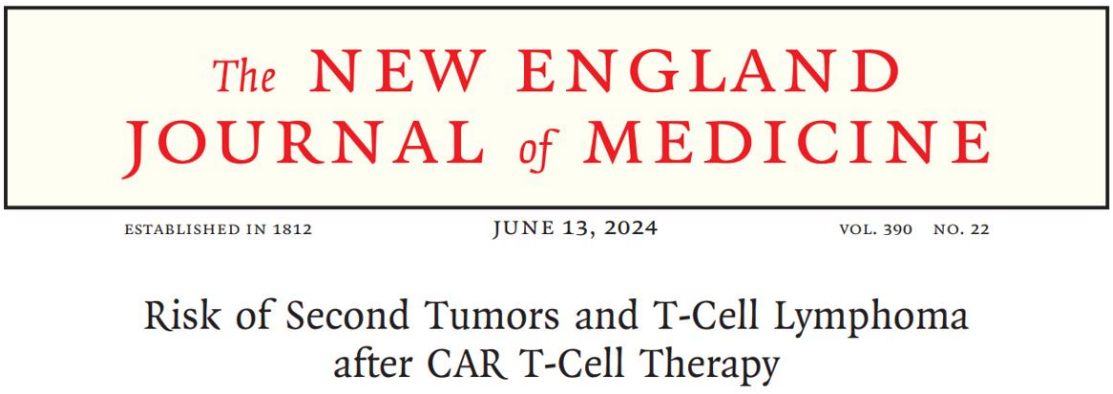
3. How black box warnings affect cell therapy

For any drug or therapy, the most important factor is the benefit/risk ratio. Currently, cell therapy has saved many terminal patients who had no other treatment options available. Cell therapy provides significant survival benefits, so the black box warning may not have a substantial impact.

On the other hand, secondary lymphoma is common among cancer patients, and there is no clear evidence to establish a direct correlation between cell therapy and lymphoma. However, as cell therapy seeks new indications, such as for autoimmune diseases, patients with non-life-threatening conditions may have more concerns about lymphoma risk.

4. Frequency of T-cell lymphoma

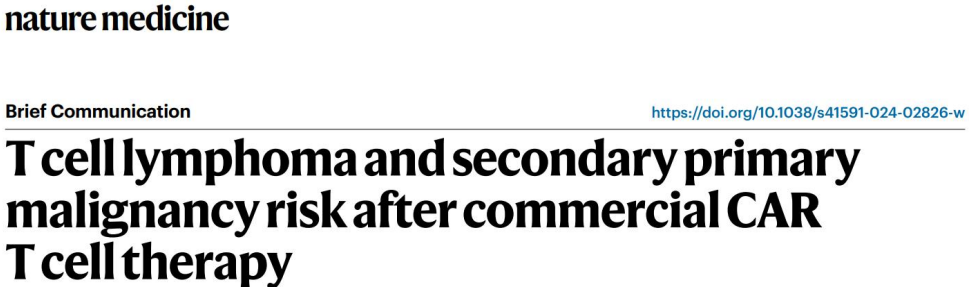
Researchers analyzed the outcomes for 724 people treated with CAR-T cell therapy at Stanford Health Care between 2016 and 2024. Among these individuals, the incidence of secondary blood cancers was approximately 6.5% over a median of three years of follow-up, which is roughly similar to patients who underwent stem cell transplantation rather than CAR-T cell therapy to treat their cancers [1].


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2024 VOL. 390 NO. 22

Risk of Second Tumors and T-Cell Lymphoma after CAR T-Cell Therapy

Another research group, including Prof. Carl June, analyzed 1,500 cases and observed no instance where integrated CAR was found in T-cell lymphoma [2].


nature medicine

Brief Communication https://doi.org/10.1038/s41591-024-02826-w

T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy

5. Impact on CAR-T production

The concern about T-cell lymphoma arises from the use of viruses for CAR expression, which is associated with the risk of genomic integration. For instance, lentiviral vectors, despite integrating in a semi-random fashion, have an affinity for areas of the genome where active gene expression is taking place, posing a risk for insertional oncogenesis. In three cases of lymphoma, the CAR transgene has been detected in the malignant clone, indicating that the product was likely involved in the development of T-cell cancer [3].

New strategies involving targeted insertion of the CAR construct to specific loci might help reduce the risk of cancer, as well as the use of mRNA-based approaches for transient expression.

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