CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY IN HEPATITIS B VIRUS–ASSOCIATED HEPATOCELLULAR CARCINOMA: CURRENT EVIDENCE AND FUTURE DIRECTIONS

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1. CLINICAL CONTEXT & BURDEN OF HBV-RELATED HCC

254 MILLION people globally living with chronic HBV

685,000 new HCC cases worldwide in 2022

597,000 HCC-related deaths in 2022

~52% of all HCC cases attributable to HBV worldwide

HIGHEST BURDEN IN EAST ASIA

~70% of HCC in East Asia linked to chronic HBV infection

WHY ADVANCED HBV-HCC REMAINS CHALLENGING

- Despite antiviral therapy, recurrence is frequent and prognosis remains poor.
- Limited response and survival benefit with current systemic therapies.
- High immunosuppressive tumor microenvironment hinders effective immune control.
- Need for novel, durable, and targeted immunotherapies.

OBJECTIVE

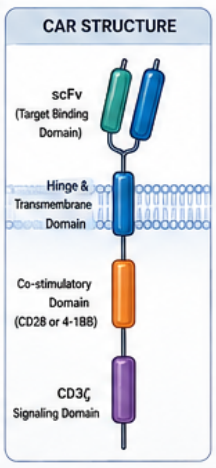
To evaluate current evidence of CAR T-cell therapy in HBV-associated HCC, focusing on therapeutic targets, clinical outcomes, safety, and future translational applications.

MATERIALS & METHODS

- Narrative review using PubMed, Scopus, Web of Science, and Google Scholar.
- Peer-reviewed studies, early-phase clinical trials, experimental data, and high-quality reviews were critically synthesized.

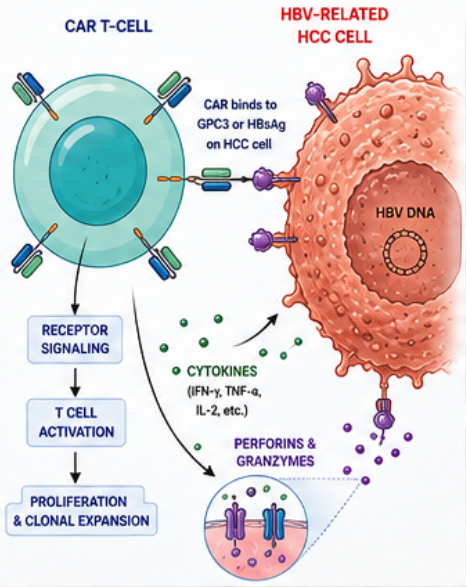
2. MODE OF ACTION OF CAR T-CELL THERAPY IN HBV-RELATED HCC

CAR STRUCTURE



1. **LEUKAPHERESIS** — Collection of T cells from patient
2. **T CELL ACTIVATION** — In vitro activation with beads/ cytokines
3. **CAR ENGINEERING** — Gene transfer to express CAR
4. **EXPANSION** — Ex xivo expansion of CAR T cells
5. **INFUSION** — CAR T cells infused back into patient

6 TARGET RECOGNITION & CELLULAR INTERACTION



7 ACTIVATION & KILLING MECHANISMS

A CYTOKINE-MEDIATED EFFECTS

- Inhibition of proliferation
- Induction of apoptosis
- Anti-angiogenic effects
- Immune modulation

B PERFORIN / GRANZYME PATHWAY

Perforin forms pores in tumor cell membrane

Granzymes enter and activate caspases

C PROGRAMMED CELL DEATH: APOPTOSIS

Caspase activation
DNA fragmentation & & clearance

OUTCOME: Specific elimination of GPC3/HBsAg-expressing HBV-related HCC cells, reduction in tumor burden and improved anti-tumor immunity.

3. CLINICAL EVIDENCE (EARLY-PHASE STUDIES)

OBJECTIVE RESPONSE RATE (ORR)
15% – 50%
Across early-phase studies targeting GPC3

DISEASE CONTROL RATE (DCR)
23% – 91%
Across early-phase studies targeting GPC3

MEDIAN PROGRESSION-FREE SURVIVAL
3 – 8 MONTHS
In patients with advanced HCC

PRINCIPAL TARGET

Glypican-3 (GPC3) expressed in ~70–80% of hepatocellular carcinomas

SAFETY PROFILE

- Cytokine release syndrome (CRS) most common adverse event
- Predominantly Grade 1–2
- Severe neurotoxicity uncommon

4. CURRENT LIMITATIONS / CHALLENGES

- Heterogeneous antigen expression and tumor escape
- Immunosuppressive tumor microenvironment (Tregs, MDSC cells) exhausted T cells)
- On-target off-tumor toxicity (e.g., GPC3 in normal tissues)
- Poor T cell trafficking and penetration into solid tumors
- Limited persistence of CAR T cells
- High cost and complex manufacturing

5. FUTURE DIRECTIONS

- Dual-target CARs (e.g., GPC3 + HBsAg) to overcome antigen heterogeneity
- Cytokine-armored CAR T cells to enhance persistence and efficacy
- Combination strategies with immune checkpoint inhibitors or anti-angiogenic agents
- Regional delivery approaches (e.g., hepatic artery infusion) to improve trafficking
- Biomarker-based patient selection and real-time monitoring
- Off-the-shelf / allogeneic CAR T cells for broader accessibility

6. CONCLUSION

CAR T-cell therapy represents a rapidly evolving treatment strategy for HBV-associated hepatocellular carcinoma. Although current evidence is primarily derived from preclinical investigations and early-phase clinical studies, advances in cellular engineering continue to address the biological limitations associated with solid tumors. Further prospective clinical trials are required to establish long-term efficacy, optimize patient selection, and define the role of CAR T-cell therapy within multidisciplinary management of HBV-related HCC.

KEY TAKE-HOME MESSAGE

CAR T-cell therapy targeting GPC3 and HBsAg holds transformative potential for HBV-associated HCC, but optimized strategies and robust clinical validation are essential for durable success.

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ABBREVIATIONS

HBV: Hepatitis B Virus
HCC: Hepatocellular Carcinoma
CAR: Chimeric Antigen Receptor
ORR: Objective Response Rate
DCR: Disease Control Rate
PFS: Progression-Free Survival
CRS: Cytokine Release Syndrome