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Current Landscape and Prospects of CAR-T Cell Therapy in Prostate Cancer: A Clinical Trial Review

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Abstract: This review talks about the causes and dangers of prostate cancer. The widespread of prostate cancer and the shortcomings of traditional therapies are discovered, and the principles, significance, and prospects of CAR-T therapy were discussed. Through discussing the significance of CAR-T therapy and the progress of clinical trials. This paper talks about the relevant targets of CAR-T therapy for prostate cancer such as PSMA, PSCA, reviews the purpose, process and results of currently approved clinical trials. This review hopes to find the focus and shortcomings of current CAR-T therapies in the clinical trials and contributes to the development of more efficient CAR-T therapies.

Keywords: prostate cancer, CAR-T, clinical trial

1. Introduction

Cancer remains one of the most critical health challenges worldwide, affecting millions in both the 20th and 21st centuries, with incidence rates continuing to rise globally [1]. The primary causes of cancer include cellular division errors, DNA damage, and inherited genetic factors. Cancer is widespread, and approximately one in four individuals is estimated to have a lifetime risk of developing the disease.

Among various cancers, prostate cancer is currently the most frequently diagnosed cancer among men in developed countries and is becoming increasingly common globally [2]. Standard treatment options for prostate cancer include radiotherapy, surgery, and chemotherapy, as well as advanced approaches like gene therapy, stem cell therapy, antioxidant-based therapies, and targeted therapies [3]. However, these treatments are not always effective, especially in advanced cases. Metastatic castration-resistant prostate cancer (mCRPC) represents an aggressive form of prostate cancer that does not respond to traditional hormonal treatments [4].

Chimeric Antigen Receptor T-cell (CAR-T) therapy, a targeted immunotherapy, has shown remarkable clinical responses in certain types of hematologic malignancies, particularly subsets of B-cell leukemia and lymphoma. However, the application of CAR-T cell therapy to solid tumors, including prostate cancer, has proven challenging, with limited success to date [5]. Despite these challenges, CAR-T therapy remains a promising approach, and there is growing interest in its potential for prostate cancer treatment [6].

This review aims to summarize the current clinical trials investigating CAR-T cell therapy for prostate cancer and to explore the specific challenges and obstacles that need to be addressed to improve its efficacy. The clinical trials database indicates that only one out of fifteen trials has

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reported results thus far, with most trials focusing on the Prostate-Specific Membrane Antigen (PSMA) as a target.

2. Patient population

Most clinical trials on CAR-T cell therapy for prostate cancer are conducted in various states across the United States and China, with two trials located in Germany and Malaysia. Recruitment criteria for these trials are carefully designed to ensure the safety and relevance of participants, who must be informed of potential risks and willingly consent to participate.

In general, subjects in these trials are required to be adults, often aged 18 and above, with an upper age limit in some cases. Most trials specifically enroll male participants, given the focus on prostate cancer. Eligibility criteria typically include confirmation of diagnosis through tumor biopsy and evaluation by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and the Prostate Cancer Working Group 3 (PCWG3) guidelines. Participants are also required to use contraception and avoid direct semen contact during the study.

To ensure participants can safely complete the trials, they must meet specific health criteria, such as adequate vital organ function and normal blood parameters, as certain conditions (e.g., heart failure or cachexia) could significantly impact study outcomes. Additionally, participants should exhibit high expression levels of the target antigen relevant to CAR-T therapy, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, although some trials may accept an ECOG status up to 2. Trials that use intravenous administration often require patients to have stable venous access.

Candidates are generally those for whom standard treatments have proven ineffective, though not necessarily treatment-resistant. Patients with conditions that could adversely impact trial progress are usually excluded. For instance, individuals with other high-risk malignancies (excluding low-risk tumors) or prostate cancer with neuroendocrine differentiation or mixed histology are typically not eligible. Other exclusion criteria include autoimmune diseases, infectious diseases (e.g., HIV, HBV), active systemic infections, significant central nervous system disorders (e.g., epilepsy), severe ophthalmologic conditions, and recent major surgeries.

To prevent potential complications, individuals with severe organ dysfunction, such as advanced liver or lung disease (especially with airway obstruction risk), are excluded. Patients with a history of previous CAR-T therapy, recent anti-cancer or immunosuppressive drug treatment, or those with inadequate T-cell availability are also not eligible. Additionally, patients are excluded if they have a recent history (within six months) of intracranial hemorrhage, vaccinations, or stroke, as well as those with uncontrolled psychiatric conditions, which may affect trial communication.

In some cases, weight restrictions are applied, and those who have participated in other trials are excluded to maintain consistency and minimize interference with results.

3. Targets of CAR-T Cell Therapy

Current clinical trials in CAR-T cell therapy for prostate cancer are focused on several targets, including Prostate-Specific Membrane Antigen (PSMA), Prostate Stem Cell Antigen (PSCA), Kallikrein-Related Peptidase 2 (KLK2), Six-Transmembrane Epithelial Antigen of Prostate 1 (STEAP1), and L1 Cell Adhesion Molecule (L1CAM), among others.

PSMA

PSMA is a transmembrane glycoprotein specifically and highly expressed in prostate cancer (PCa), with expression levels correlating with tumor aggressiveness [7]. Structurally, PSMA consists of 750 amino acids and has three domains: a 19-amino acid intracellular domain, a 24-amino acid transmembrane domain, and a 707-amino acid extracellular domain, which contains multiple

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antigenic epitopes capable of ligand binding [8]. Most PSMA-targeted CAR-T cell trials (NCT05354375, NCT05732948, NCT04429451, NCT01140373, NCT04633148) focus on determining optimal dosing, maximum tolerated doses, and evaluating side effects and efficacy by tracking PSA levels and other biomarkers. Although preclinical and early clinical studies have shown PSMA-targeted CAR-T cells can be effective against PCa, their clinical application has encountered challenges due to unexpected toxicities, including cytokine release syndrome (CRS), neurotoxicity, and allergic reactions [9].

Some trials are exploring the combination of PSMA-targeted CAR-T cells with anti-PD1 therapy to enhance efficacy. PD1 and its ligand PDL1 are immune checkpoints that can enable tumors to evade immune responses and prevent CAR-T cells from reaching tumor cells [10]. Thus, combining PD1 inhibitors with anti-PSMA CAR-T cells may enhance treatment outcomes by blocking this immune suppression pathway.

PSCA

Prostate Stem Cell Antigen (PSCA) is a glycosylphosphatidylinositol (GPI)-anchored cell surface protein frequently overexpressed in prostate cancer cells [11]. PSCA can play a dual role, acting as both an inhibitor of cell proliferation and a promoter of tumorigenesis. Studies have shown that PSCA overexpression enhances the proliferation, migration, and invasion of PCa cells in vitro and promotes lung metastasis in vivo, partly through the regulation of IL-6 via the p38/NF-κB signaling pathway [12]. Given its role in PCa progression, PSCA has potential both as a diagnostic marker and a therapeutic target [13]. Some trials are also testing the combination of PSCA-targeted CAR-T therapy with PD1/PDL1 inhibitors to reduce tumor resistance and improve efficacy.

KLK2

Kallikrein-Related Peptidase 2 (KLK2) is another promising target in early clinical development, as it is specifically expressed in prostate cancer [14] and plays a role in the complex tumor microenvironment [15]. KLK2 shares 78% sequence homology with PSA and is detected at various expression levels in prostate cancer: 23% of cases show no expression, 38% show weak expression, 35% moderate expression, and 4% strong expression [16]. KLK2 is involved in extracellular matrix degradation, local invasion, cancer cell proliferation, and angiogenesis [17], making it a valuable target and biomarker for PCa.

STEAP1 and STEAP2

The STEAP (Six-Transmembrane Epithelial Antigen of the Prostate) family, particularly STEAP1 and STEAP2 [18], is overexpressed in several cancers, including prostate cancer, and is being explored in CAR-T cell therapy trials. High STEAP1 expression is associated with poorer survival outcomes in prostate cancer patients [19]. A Phase 1 trial has reported promising results with an antibody-drug conjugate targeting STEAP1 in metastatic castration-resistant prostate cancer [20]. STEAP2 is also significant in prostate cancer, as its overexpression promotes PCa cell proliferation [21]. Unlike STEAP1, STEAP2 does not show a significant correlation with age or PSA levels, making it a potentially reliable target in stratified analyses [22].

L1CAM

L1 Cell Adhesion Molecule (L1CAM) is another target considered in CAR-T cell therapy trials for prostate cancer. L1CAM is overexpressed in various cancers and is often associated with poor prognosis, which supports its inclusion as a therapeutic target [23].

4. Purpose and Outcome Measures of CAR-T Trials

The primary aim of these CAR-T cell therapy trials is to gather data to assess the therapy's safety and efficacy in prostate cancer treatment. The primary outcome measures across these trials can generally be categorized into three key factors:

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1. Incidence of Adverse Events: This includes monitoring the types, severity, and frequency of adverse events, providing crucial information on the therapy's safety profile.
2. Dose-Limiting Toxicity (DLT): DLT refers to specific adverse events that limit the dosage a patient can tolerate, such as high-grade non-hematologic toxicities or significant hematologic toxicities. Recording DLT rates helps to identify the upper safety threshold of the therapy.
3. Maximum Tolerated Dose (MTD): The trials aim to establish the highest dose that patients can tolerate without unacceptable side effects. MTD determination is vital for setting safe dosage guidelines in clinical applications.

Most trials primarily focus on safety as their primary outcome measure. Secondary outcome measures, however, vary between trials and are geared towards evaluating the therapy's effectiveness and antitumor activity. Common secondary outcomes include:

- Overall Response Rate (ORR) and Disease Control Rate (DCR): These metrics assess the therapy's efficacy in reducing tumor size and halting disease progression.
- Antibody Production: Some trials track the number of participants who produce antibodies in response to CAR-T cell therapy, as this may influence long-term efficacy and safety.

Additionally, pharmacokinetic data, such as the maximum plasma concentration of the therapy and the time to reach that concentration, are recorded to understand the therapy's absorption and processing in the body. Other important measures include:

- Response Duration and CAR-T Cell Persistence: Tracking the duration of response and the number of CAR-T-positive cells over time allows for assessment of the therapy's durability and scalability.
- Overall Survival Rate and Time: Overall survival rates and times, often measured at specified intervals unique to each trial, serve as critical indicators of long-term effectiveness.

These comprehensive outcome measures enable a thorough evaluation of CAR-T cell therapy's potential in treating prostate cancer and its viability as a therapeutic option.

5. Results Summary

Most CAR-T cell therapy trials for prostate cancer have not yet yielded results, even though some have completed data collection. Approximately 10% of these trials have reported outcomes, with trial NCT03873805 providing the most comprehensive data.

In trial NCT03873805, participants were divided into three dose levels:

- Dose Level 1: 100 million CAR-T cells.
- Dose Level 2: 100 million CAR-T cells with lymphodepletion, including cyclophosphamide (500 mg/m² IV) and fludarabine (30 mg/m² IV).
- Dose Level 3: 100 million CAR-T cells with modified lymphodepletion, using a reduced dose of cyclophosphamide (300 mg/m² IV) and fludarabine (30 mg/m² IV).

Each cohort consisted of American white males, with 3 participants in Dose Level 1, 6 in Dose Level 2, and 5 in Dose Level 3. Baseline PSA levels increased progressively with higher dose levels, reflecting the escalating treatment intensities.

Primary Outcome: Toxicity Profile (Grade 3 Adverse Events, up to 32 Months)

- Anemia: Observed in 2 participants in both Dose Level 1 and 2, but not in Dose Level 3.
- Lymphopenia: Experienced by participants in Dose Levels 1 and 3 but not in Dose Level 2.
- Fatigue, Pain, Hematuria, and Cystitis: Only participants in Dose Level 2 reported these symptoms.
- Dose-Limiting Toxicities (DLTs): Two participants in Dose Level 2 experienced DLTs, whereas no DLTs were reported in Dose Levels 1 or 3.

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Secondary Outcomes

- CAR-T Cell Persistence at Day 28: Persistence rates were similar across doses, with 66% in Dose Levels 1 and 2, and 60% in Dose Level 3. CAR-T cell expansion was highest in Dose Level 2 and lowest in Dose Level 1.
- Disease Stabilization and Survival Rates:
  - Dose Level 1 had no participants with disease stabilization, and a 6-month survival rate of 33%.
  - Dose Level 2 showed better outcomes, with a 6-month survival rate of 67%.
  - Dose Level 3 had a 6-month survival rate of 40%.
- All-Cause Mortality Risk: All participants were at risk of all-cause mortality.

Adverse Events

- Dose Level 1: Two participants experienced serious adverse events, including systemic edema and urinary tract infection.
- Dose Level 2: Two participants reported abdominal pain and ileus.
- Dose Level 3: Four participants experienced serious adverse events, including cytokine release syndrome (CRS), septicemia, limb pain, and stroke.

Across all dose levels, adverse events of varying severity were observed, with the lowest incidence in Dose Level 1. However, Dose Level 2 demonstrated a favorable balance of efficacy and manageable toxicity, suggesting a potentially optimal dose level for future trials.

6. Conclusion

Currently, there are limited clinical trials exploring CAR-T cell therapy for prostate cancer, but early research data suggests promising potential. While existing trials have shown that CAR-T therapy can induce meaningful responses in certain cases, the challenges of targeting solid tumors, particularly overcoming immune suppression within the tumor microenvironment, remain significant.

Future advances in CAR-T therapy for prostate cancer will likely depend on identifying novel targets and developing strategies to enhance CAR-T cell persistence and efficacy. Continued research is essential to optimize this approach, addressing barriers to effectiveness, reducing toxicity, and ultimately improving outcomes for patients with prostate cancer.

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