Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/60/20241433

Advancing the Frontiers of Oncology: The Promising Horizon of CAR-T cell therapy for colon cancer

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Abstract. In the changing field of cancer treatment, cancer immunotherapy shines as a promising method that uses the body's own immune system to fight against cancer. This review investigates how this therapy works and its possibilities, with special attention given to CAR-T cell therapy for colon cancer. We investigate why immune checkpoint inhibitors work, what happens when we use cancer vaccines and especially CAR-T cell therapy - showing their victories as well as difficulties encountered along the way particularly within solid tumor treatments. The future of CAR-T cell therapy in colon cancer and the current clinical trials to tackle these hurdles are explained thoroughly.

Keywords: CAR-T cell therapy, Colon cancer, Immunotherapy.

1. Introduction

Cancer immunotherapy is a major step in the field of oncology, giving hope that goes beyond usual methods like surgery, chemotherapy, and radiation. This fresh approach strengthens body's immune system to recognize and eliminate cancer cells. The focus of cancer immunotherapy is on enhancing the natural power of our immune system, which could potentially offer a safer and better choice compared to normal treatments for cancers.

2. Types of Cancer Immunotherapy

At the heart of cancer immunotherapy, there are three main types: immune checkpoint inhibitors, cancer vaccines and cell-based treatments. Each type works in a different way that helps the immune system fight against cancer. For instance, immune checkpoint inhibitors stop certain proteins from making the immunity less active so it can identify and destroy malignant cells again [9]. This is a very important aspect of how the immune system can be used to fight against cancer. The "revitalization" of the immune reaction, especially with the help from these new types of drugs called immune checkpoint inhibitors, shows great promise in many kinds of cancers like those found in kidneys, lungs, and melanoma. This shows that this method has been proven effective for various types of cancer [10]. These vaccines are designed to instruct the immune system on specific components that are exclusively present on cancer cells, thereby triggering an immune response. This is an active method for treating and preventing the escalation of severity by utilizing the body's inherent ability to concentrate its defense on specific targets [3]. Another strategy in cancer immunotherapy, cell therapy, is focusing on strengthening a patient's immune cells for better identification and removal of cancer cells. A well-known example of this is CAR-T (chimeric antigen receptor T-cell) therapy. It starts by taking T-cells from the patient, then

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changing them with genes so they can express CARs that are made to target antigens specific to cancer. After these improved cells have been returned into the patient's body again [12, 5]. This method has significantly enhanced results in several hematological malignancies, establishing CAR-T cell therapy as a leader among customized methods for treating cancer[8].

3. Colon Cancer and CAR-T Cell Therapy

Colon cancer is a serious problem for public health. It happens because cells in the mucosal layer of the colon or rectum start to grow uncontrollably. The chance of getting this cancer can be affected by many things, like how old someone is, their family history with diseases and lifestyle choices such as what they eat[7]. Even with progress in treatments for cancer worldwide, there are still many cases of colon cancer that need to be treated. This shows that better and more effective treatments are still needed[12].

4. Challenges and Future Directions

The study of CAR-T cell therapy in the field of colon cancer shows a hopeful direction for immunotherapy, possibly starting a fresh time with good treatments. The advantages from CAR-T cell therapy are big but there are also troubles. Things like bicistronic CARs, TanCARs, LoopCARs and allogeneic "off-the-shelf" CAR-T cells try to improve how well this therapy can stop cancer spreading and its ability to hit tumors correctly. The introduction of fourth- and fifth-generation CARs, which include more transcription factors and stimulating domains, shows the continuous effort to make CAR-T cell therapy better at fighting cancer. The studies that keep working on GD2 and HER2 in solid tumors are expected to give important understandings. Yet, the differences of solid tumors make it hard to find universal tumor antigens. This is made more complex by how the tumor microenvironment can suppress immune responses. The success rates for CAR-T cell therapy in dealing with solid tumors are not as high as those for blood-related cancers. This shows the difficulties involved in applying this treatment approach to contexts involving solid tumors such as colon cancer.

5. Clinical Trails

This manuscript highlights the importance of research efforts in tackling these difficulties to improve treatment results. Phase 2 clinical trials are very significant, especially to assess the safety and effectiveness of therapies on a broader level than Phase 1 studies. The study about using CAR-T cell therapy for colon cancer is crucial in phase two trials because it helps understand how well this new method may work when dealing with solid tumors like those found in colon. The continuous clinical trials on ClinicalTrails.gov are examining the usage of CAR-T cell therapy in treating colon cancer. Here is a summary of them:

1). Solid Tumor Analysis using Logic-Gated CAR-T, A2B694.

The A2B694 clinical trial has a goal to study a new CAR-T cell therapy for solid tumors. This could be colorectal, pancreatic, lung and ovarian cancer along with mesothelioma in patients whose tumors show mesothelin (MSLN) but don't have HLA-A*02 expression. The therapy is still in progress through an ongoing phase 1/2 study that plans to determine safety and best dose of A2B694 after Preconditioning Lymphodepletion regimen during phase 1; while phase 2 dedicates itself towards effectiveness assessment by selectively eliminating tumor cells without affecting normal ones. This specific targeting might substantially reduce harm to regular tissue, which is a common worry with available treatments for solid tumors. The main results of the study include the rate at which adverse events and dose-limiting toxicities happen, as well as what is known as the recommended phase 2 dose (RP2D). These are investigated using Common Terminology Criteria for Adverse Events from Cancer Therapy Evaluation Program and cytokine release syndrome. The study also looks at how people react after getting an infusion by measuring overall response rate in their bodies using RECIST v1.1 criteria. The other important results are about how long A2B694 CAR-T cells stay in the body, which is checked by PCR method, and studying cytokines present like interferon-gamma and interleukin-6 levels through blood samples taken from those who received treatment. All these details suggest a complete method for testing. The objective is to explore the endurance of the treatment's effect and the immune response from

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human bodies, with evaluations arranged until 24 months after infusion. People are first asked to join in BASECAMP-1 study so that T-cells can be gathered, processed, and later infused back into them once they have finished PCLD regimen. This process could possibly offer a safer and better treatment option for patients having such types of cancers that usually only receive palliative care treatments. It was predicted that this study would begin in March 2024 and its estimated completion time is by June 2029. The work shows a dedication to making drugs that can tell apart good cells from bad ones, creating a therapeutic window which has potential for changing how we control advanced solid tumors [1].

2). Cadherin 17 research CAR T-cell Treatment CHM-2101.

The CHM-2101 clinical trial's purpose is to study CHM-2101, an autologous Cadherin 17 (CDH17) CAR T-cell therapy. It aims at checking the safety and effectiveness of this therapy in people with advanced gastrointestinal malignancies who didn't see any improvement from one standard treatment method. This experimental medicine goes through a careful phase 1/2 trial for finding out what dose is safe and works well after lymphodepletion. In Phase 1, we mainly investigate how much dosage can be tolerated by patients while also searching for dose-limiting toxicities (DLTs). Meanwhile, Phase 2 involves confirming the treatment's ability to work as described - it should specifically target and render cancer cells inactive without damaging normal ones. This focused targeting is expected to greatly decrease harm to normal tissue, a significant problem with existing methods for treating advanced gastrointestinal malignancies. The primary results that will be examined include dose-limiting toxicities and the overall response rate (ORR) based on RECIST v1.1 criteria. The secondary outputs measure how well this therapy controls disease growth along with its effect on patient survival; these are disease control rate (DCR), time until response occurs or TTR, duration of response DOR), progression-free survival PFS), and overall survival OS). The outcome metrics provide a comprehensive view of what the treatment can achieve, considering immediate effects as well as those lasting up to 15 years following infusion. It was thought that this study would begin in June 2024 and finish around June 2027. The method of this trial is broad, going from the first stage of gathering cells to later follow-ups over time. This offers a complete assessment on how safe and effective the therapy can be [6].

3). PSMA/CD70 Bi-Specific CAR-T Study: Targeting CD70 and PSMA Positive Malignancies.

The trial is about a fresh anti-PSMA/CD70 bi-specific CAR-T cell treatment, meant for people with malignancies that have both CD70 and PSMA. This inventive therapy method changes T cells with the help of 4th generation lentiviral vectors to recognize and fight cancerous cells expressing either CD70 or PSMA. These antigens are highly increased in various kinds of cancers such as kidney, breast and prostate tumors but they show up only minimally in healthy tissues making them suitable targets for therapeutic therapy. The purpose of the study is to understand if this CAR-T cell treatment that targets two things at once can be done and it's safe, especially looking into how long these modified T cells stay working in patients. The trial will use a planned out plan called protocol to watch for bad effects happening in a certain number of patients as main measurement of toxicity for six months, using Common Toxicity Criteria for Adverse Effects version 4.0. Other results they will observe are responses from complete or partial remission of tumors over one year using the RECIST v1 criteria, along with how much these T cells grow and last in patients (expansion and durability). Assessing will be done by using CAR copies scale for efficacy and tumor burden scale. The experiment will also see overall survival (OS) and progression-free survival (PFS) rates after three years. This trial is a big step forward in cancer treatment, showing promise for dealing with resistant or recurring malignancies that have limited therapy choices. The therapy aims to reduce the escape routes of tumor by focusing on two antigens simultaneously. This could result in better results for patients who have CD70 and PSMA positive malignancies [11].

4). Testing A2B530 (autologous logic-gated Tmod CAR-T cell product) in Subjects with Solid Tumors.

This study is about the safety and effectiveness of A2B530, an autologous logic-gated Tmod CAR-T cell therapy. It focuses on adult patients who have solid tumors such as colorectal cancer, pancreatic cancer or non-small cell lung cancers that express carcinoembryonic antigen and possess a somatic loss of HLA-A02 expression. The research is split into two parts. Phase 1 is about finding the highest safe

DOI: 10.54254/2753-8818/60/20241433

dose of A2B530 and examining adverse events, along with DLTs by dosage level. This evaluation uses Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTEP-CTCAE), version 5.0 for CRS and ICANS. RP2D, or Recommended Phase 2 Dose, gets decided in a period of 21 days after the infusion of A2B530 through Bayesian Optimal Interval (BOIN) research design which considers both safety aspects as well as biomarker information. Phase 2 checks how well it works using ORR or Overall Response Rate that's measured by RECIST v1.1 standards and reviewed independently at central location after 24 months from when you had your infusion session with A2B530 Additional results involve the persistence of A2B530, counted by Polymerase Chain Reaction (PCR) on patient blood samples to gauge the number of Tmod CAR T cells present in participants. Also, cytokine analysis measures levels in patients treated with A2B530 for up to 24 months after infusion as secondary endpoints. The process to harvest and store T cells needs around 160 participants who first complete the BASECAMP-1 trial. These cells are then turned into A2B530 treatment and given back through reinfusion into patients as their disease advances. This fresh method, that started on April 28th of year 2023 and should finish by December 2028, hopes to give a different type of treatment choice for advanced solid tumors. It might show much better safety and effectiveness than the current treatments. The novel approach uses a special process where they first lessen lymphocytes with conditioning therapy before giving A2B530 Tmod CAR-T cells [1].

5). CNA3103 Study Administered to Subjects with Metastatic Colorectal Cancer

The clinical trial CNA3103 is a study that examines the safety and effectiveness of a new treatment for metastatic colorectal cancer. This method uses LGR5-targeted Autologous Chimeric Antigen Receptor (CAR)-T Cells as its main feature. This Phase 1/2a trial focuses on checking the administration of one dose through an intravenous line in CNA3103, with key aim to evaluate treatment's safety profile and best response over span of 24 months. The participants are chosen carefully by undergoing pre-screening process to ensure they have LGR5 expression required for the trial, then they go through strict screening processes such as leukapheresis (T cell collection) and lymphodepletion by chemotherapy before receiving CAR-T cell therapy. The trial has two parts: the Phase 1 section, which deals with dose escalation and uses a Bayesian Optimal Interval (BOIN) design to decide Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D); this assures that participants are exposed to minimal risk while finding best dosage. The second part is Phase 2a, focusing on dose expansion. This segment aims to enroll more participants at the MTD/RP2D level for studying CNA3103's safety, pharmacokinetics, pharmacodynamics and anti-tumor activity. Secondary study results involve the frequency of treatment-emergent bad events, detailed pharmacokinetics determined by counting CNA3103 cells in patient's blood plus survival rates up to twenty-four months after treatment. Additionally, the study also intends to find out the RP2D by using observed DLTs within 28 days of infusion as a guide for dose escalation or de-escalation. It will watch out for replication-competent viral constructs and assess how long patients can stay without progression in their disease (progression-free survival). This last measure is very important because it focuses specifically on any failures to treat that may happen due to issues in manufacturing or patient-related factors within 8 weeks' time frame. This trial represents a big step forward in making new targeted treatments available for people with metastatic colorectal cancer. It gives hope for better and safer treatment options by intelligently applying CAR-T cell technology [4].

6. Conclusion

This review deeply explores the growing area of cancer immunotherapy, showcasing the groundbreaking power of CAR-T cell therapy in colon cancer treatment. It carefully explains the mechanisms and promises of different immunotherapeutic plans from immune checkpoint inhibitors to vaccines for treating cancers along with CAR-T cell therapy which can restructure a patient's immune cells for attacking and removing cancer cells. This method provides an innovative way to treat cancer that surpasses current standard methods. Although CAR-T cell therapy has shown outstanding results in treating blood-related cancers, using it for solid tumors like colon cancer has encountered real difficulties. This is because of the varied nature of tumors and the immune-suppressing environment

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found within them. The review also investigates clinical tests that are presently being conducted, which are leading the way in introducing new methods to overcome these obstacles. This demonstrates how CAR-T cell therapy is changing and its potential to redefine how we treat colon cancer. The review looks closely at these advanced trials, highlighting how crucial it is to continue researching and experimenting in clinical settings for fully using CAR-T cell therapy's potential in oncology field.

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