GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 6 (339) Июнь 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 6 (339) 2023

Содержание:

GEORGIAN MEDICAL NEWS
No 6 (339) 2023

THE ROLE OF IMMUNOTHERAPY IN CANCER TREATMENT: CHECKPOINT INHIBITORS, CAR-T CELLS, AND VACCINES

Jagdish Kumar Arun[1], Ashok Kumar Singh[2], Shashidhar ES[3], Geetika M. Patel[4], Yogita Verma[5], Samir Sapcota[6].

[1]*Professor, Department of Pharmacy, Vivekananda Global University, Jaipur, India.*

[2]*Associate Professor, Department of General Surgery, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India.*

[3]*Assistant Professor, Department of Forensic Science, School of Sciences, JAIN (Deemed-to-be University), Karnataka, India.*

[4]*Associate Professor, Department of Community Medicine, Parul University, PO Limda, Tal. Waghodia, District Vadodara, Gujarat, India.*

[5]*Tutor, Department of Nursing, IIMT University, Meerut, Uttar Pradesh, India.*

[6]*Assistant Professor, Department of Ayurveda, Sanskriti University, Mathura, Uttar Pradesh, India.*

Abstract.

Immunotherapy causes cancer patients' immune systems to activate in search of and eliminate cancer cells. As a therapeutic area for cancer, it has expanded in importance and demonstrated promising results in treating many cancers. Checkpoint blockade (CPB) therapy may stimulate a suppressed immune response to provide long-lasting therapeutic results. However, the absence of a tumor-reactive immune infiltration is probably why response rates are still low. Using chimeric antigen receptor (CAR)-modified T cells to fight cancer may significantly impact immunology. This study explored using checkpoint inhibitors, car-T cells, and vaccines in immunotherapy to treat cancers. Drugs used for CPB aim to reduce immunological suppression, allowing for more effective CAR T cells and dendritic cell (DC) vaccines, providing some optimism that this may be increased, both of which have proven therapeutic efficacy in specific cancers. However, drug-induced side effects and the tumor microenvironment's propensity for immunosuppression mean treatment effectiveness is still inadequate. The outcomes of current preclinical tests suggest that novel therapies targeting lymphocyte-activation gene 3 (LAG3), T cell immunoglobulin and mucin-domain containing-3 (TIM3), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and programmed cell death protein 1 (PD-1) could be used as adjuvant therapies to modify the tumor microenvironment.

Key words. Immunotherapy, cancer treatment, checkpoint inhibitors, CAR T cells, oncolytic viruses, DC vaccines.

Introduction.

In the last few years, immunotherapy has been the focal point of ground-breaking research and development for cancer therapies. New, promising treatments for tumors with poor prognoses have been approved more rapidly than with traditional medicine, and the cancer care landscape is quickly and constantly shifting. There have been several pivotal people and significant advances in the field of immunotherapy for cancer treatment since its inception [1]. Cell-mediated cytotoxicity involves the release of cancer cell antigens, delivery to antigen-presenting cells (APCs), successful presentation to T cells, priming and activation of APCs and T cells, trafficking and infiltration of antigen-specific T cells into tumors, recognition of cancer cells by T cells, and overriding immunosuppression in the tumor microenvironment [2]. Due to the advancement of tumor immunotherapy in the clinic, combining vaccination with immune checkpoint inhibitors (ICI) is a newly developed method for treating cancer. The complete immunological response is still a problem, however. A genetically modified cell membrane nanovesicle that combines immunosuppression reversal with antigen self-presentation for enhancing cancer immunotherapy. It is a detailed illustration of a customized vaccine formulation that instantly activates both naïve and worn-out T cells.

The artificial nano vaccine has excellent homing properties, higher durability, and a nanoscale size that may quickly fill the lymphatic system. Compared to traditional vaccinations, this particular antigen self-presentation method is better. The anti-PD1 medication, which boosts T cell immune response and breaks immunosuppression, is crucially administered to B7 codelivery initially [3]. Many immediately conjure up the idea of immunizations against germs and viruses when they hear "vaccine." Such immunizations have shielded humanity from deadly illnesses for a long time. By immunizing healthy individuals with attenuated or detoxicated bacteria, viruses, or other infectious antigens, vaccines protect them against disease. A vaccine's primary function is to stop or lessen the severity of infectious illnesses that are life-threatening.

Vaccine-induced immunological memory acquisition often lasts for a very long time. Multiple people have developed immunity to numerous diseases due to a successful worldwide system of regular vaccination against prevalent ailments. Since vaccines are widely considered one of the most beneficial and crucial prophylactic techniques [4], the World Health Organization (WHO) advises that they be accessible in developed countries. Late detection, the TME's molecular complexity, and a shortage of highly effective therapy options all contribute to cancer's continued status as a worldwide health crisis. There was an urgent need for innovative, efficient treatment methods to be implemented between 2015 and 2017 since there were 367,167 new instances of cancer and 165,000 fatalities worldwide. However, the clinical result still needs improvement due to drug resistance and side effects. Various strategies have been devised to minimize tumor resistance to chemotherapy, radiation, and a combination. Thus, the ideas of anticancer immunotherapy, established recently, are based on using a host's immune to control and eradicate cancer [5].

A study [6] investigated immunotherapy's present and prospective usefulness in treating "malignant pleural mesothelioma" [6]. Immune checkpoint inhibitors' efficacy has catapulted cancer immunotherapy to the forefront of cancer

treatment, which was made possible by identifying immune checkpoint molecules. There are now solid hopes for creating customized T-cell medicines and neoantigen vaccines. Around 2030, the age of ICI and customized cancer immunotherapy is anticipated [7]. The study [8] compares the mechanisms and side effects of cytotoxic medicines, targeted treatments, and immunotherapies. Small molecule inhibitors are related to targeted drugs. Checkpoint inhibitory antibodies, CAR T-cells, cancer vaccinations, and oncolytic viruses are examples of immunotherapies. Study [9] discussed these developments, difficulties, and prospective solid tumor treatment methods. They show the great potential of combining CAR-T cells with immunotherapies. Synthetic biology allows CAR-engineered T cells to treat high-risk hematological malignancies. It is now recognized that solid tumors that originate from epithelial cells do not respond to CAR therapy for several reasons [10]. Multiple immunotherapy strategies for lung cancer were covered in the present study [11], as well as CAR-T cell components, current clinical research utilizing CARs, and the several TAAs being explored as potential targets for lung cancer CAR-T cell production. The study [12] examined how immune checkpoint blockade techniques have been used with CAR T cell therapies to enhance immunotherapeutic effects while minimizing the impact of tumor heterogeneity and T-cell depletion. The research [13] examined the most recent developments in adoptive T-cell treatment, cancer vaccines, oncolytic viruses, novel cytokines, checkpoint inhibitors, and clinical studies using monoclonal antibodies. T-cell modifications using CRISPR-Cas9 technology have been the primary focus of the research because of the potential for these modifications to be exploited as immune therapeutics against cancer [14]. Exosomes from “CAR-T cells” that were engineered to target mesothelin (MSLN) were separated in this study [15], and surface expression of the "CARs and CD3" was shown, as was the overall preservation of the original T cells' features. The combination of “CAR T cell and CPB” treatments for solid tumor malignancies was a preliminary investigation study [16] that examined preclinical and clinical applications. The study presented [17] an update of current developments in the “cellular and molecular components of the TME” to pinpoint potential immunotherapy resistance mechanisms and create fresh combination approaches for cancer immunotherapy. The research [18] offered an inventory of the current clinical status of the CAR-T cell and OV treatments. Although therapeutic promise has been shown in preclinical research, CAR-T cells and OVs alone assist a limited number of patients. Study [19] examined the obstacles of overcoming resistance and recent advancements in immunotherapy to treat CRC. Microbiota is an autonomous organ that controls tumor development and treatment response. New immunotherapies, more selective, effective, and less toxic, extended patient longevity in the chemo-free period, provided they didn't cease therapy. They now concentrate on microbiota makeup to improve responses [20]. As a result, we focus on using checkpoint inhibitors, CAR-t cells, and vaccines in immunotherapy to treat cancer.

The remaining sections of this analysis are as follows: Part 2 introduces the methodology. The research results are in part 4. Part 4 contains the discussion. Part 5 includes the conclusion.

Role of Immunotherapy in Cancer Treatment Checkpoints Inhibitors.

A form of cancer therapy known as a checkpoint inhibitor targets specific immune cell proteins known as the checkpoints. These checkpoints stop the immune system from targeting the body's healthy cells. However, specific cancer cells may use these checkpoints to evade the immune system's attack. Checkpoint inhibitors aid the immune system in recognizing and attacking cancer cells by blocking these checkpoints. They are often used to treat diseases that have progressed to other body sections, including melanoma, lung and kidney cancer. The FDA has authorized several checkpoint inhibitors, including pembrolizumab, nivolumab, and atezolizumab. Usually, these medications are given intravenously at a medical facility or clinic. Fatigue, skin rash, and diarrhea are a few of the adverse effects that checkpoint inhibitors may cause. Rarely, they may result in more severe adverse effects such as colon, liver, or lung inflammation. It is crucial to discuss the possible advantages and hazards of this sort of therapy with your doctor and whether checkpoint inhibitors are a viable treatment choice for your particular form of cancer.

Immune-related Adverse Events (irAEs)

Immune-related Adverse Events (irAEs) are a group of unfavourable effects that may follow the administration of specific immunotherapy drugs that are intended to strengthen the immune system in order to combat cancer or other disorders. These occurrences occur when the immune system unintentionally targets healthy tissues and organs, which can have a variety of potentially grave or even fatal adverse consequences. Immunotherapy, in contrast to conventional chemotherapy, targets the immune system rather than cancer cells directly, giving rise to a different class of adverse responses known as irAEs. The effects of common irAEs on the skin, gastrointestinal tract, liver, lungs, endocrine system, or other body organs might range greatly in severity. In order to preserve patient wellbeing and ensure the safety and efficacy of immunotherapy treatments, managing and monitoring irAEs is essential. This frequently necessitates quick action.

CAR-T cell.

CAR-T cell treatment is cancer immunotherapy that uses the patient's own genetically engineered T cells. It's possible that T cells, a kind of immune cell, may identify and eliminate cancer cells and other "foreign" cells. In CAR-T cell treatment, the patient's T cells are taken from their blood and modified genetically to surface-express a chimeric antigen receptor. These receptors are designed to identify and bind to specific surface proteins malignant cells produce. Reintroduced T cells have been genetically altered to target and destroy cancer cells that produce a particular protein. Positive results have been seen when using CAR-T cells to treat blood cancers, including leukemia and lymphoma. Fever, fatigue, and low blood pressure are all possible outcomes of cytokine release syndrome, one of the dangers and side effects. It is also still a very novel and challenging kind of treatment.

Vaccination.

Immunotherapy takes the form of cancer vaccines, which prime the immune system to target and kill cancer cells. Therapeutic and preventive cancer vaccines are the two main types. By focusing on viruses or other elements that potentially raise the chance of getting cancer, preventative cancer vaccinations aim to stop certain kinds of diseases. Vaccines against infectious agents that may lead to cancer, such as hepatitis B and human papillomavirus (HPV), are becoming more common. Therapeutic cancer vaccines treat preexisting tumors by stimulating the immune system to target and kill cancer cells. Cancer cells or specific proteins or antigens found in cancer cells might be used to develop such vaccinations. Only recently have therapeutic cancer vaccines been licensed for use against some malignancies, such as melanoma and prostate cancer. They are often used in addition to other cancer treatments, including chemotherapy and radiation. Cancer vaccinations might improve the body's defenses against illness; however, this is not always the case for all people or cancer types. It is crucial to discuss the possible advantages and disadvantages of this sort of therapy with your doctor and whether a cancer vaccine is an acceptable treatment choice for your particular type of cancer. Coinhibitory pathways are often triggered during “T cell activation, the binding of T lymphocytes” to their corresponding ligands, which may inhibit anticancer immune responses. Tumor cells produce more coinhibitory ligands like PD-L1 after exposure to Th1 cytokines produced by T cells. Therefore, the production of these ligands may dampen the anticancer response, enabling the tumor to persist. Figure 1 shows that CAR T cells may be preserved using CPB with adoptive T cell therapy.

Methodology.

Cell-Extrinsic Techniques

Granzyme B expression, T cell proliferation in vitro, IFN-g production, and CAR T cell activity in vivo were all enhanced by PD-1 inhibition. In a trial using an anti-GD2 CAR, pembrolizumab treatment increased "T cell activity" and persistence after continuous antigenic activation targeting "PD-L1+ tumor cells". Anti-PD-1 CPB antibodies might help exhausted CAR T cells regain some of their effector's function. However, regular antibody delivery was necessary for the PD-1 antibody to be successful since tumor recurrence occurred when treatment was stopped.

Reducing "PD-L1 expression on MDSCs" was one way in which the "PD-L1 CPB" boosted the success of CAR T cell treatment. Adding "anti-PD-L1 antibody and MDSC-depleting antibodies" to CAR T cell therapy significantly increased its effectiveness. Since this is the case, "PD-L1+ MDSCs on CAR T cell therapy" may have suppressive effects. The systemic impact of CPB may be mitigated with the use of an "oncolytic adenovirus" encoding a "PD-L1-blocking mini-antibody" in combination with an "anti-HER2 CAR T cell" treatment. This "PD-L1 oncolytic" method reactivated "CAR T cells" better than systemic "PD-L1 antibodies" in a subcutaneous prostate cancer mouse model. Two-phase I clinical trials evaluated CAR T cells using the "PD-1/PD-L1 CPB" approach. Lymphodepletion and autologous CD19 CAR T cells cured resistant diffuse large B cell lymphoma. PD-L1 expression increased as the tumor progressed despite treatment. T cell injection day 26, patients began receiving 2 mg/kg of pembrolizumab every three weeks. By day 45, fewer PD-1/EOMES-expressing T cells were present, although CART19 cells and TCR-b T cell clones had developed.

The phase I trial comprised eleven participants with recurrent or resistant neuroblastoma. CAR T cells were administered to patients either alone (n = 4), in combination with cyclophosphamide and fludarabine (n = 4) or in combination with pembrolizumab (n = 3). No dose-limiting toxicities occurred, and all infusions were well tolerated. Pembrolizumab did not further improve the concentration or persistence of IL-15 or CAR T cell proliferation following Cy/Flu lymphodepletion. There was a complete response in one patient treated with pembrolizumab, but this is insufficient to make any conclusions. “CAR T cell” treatment has shown promising results in clinical trials in Table 1.

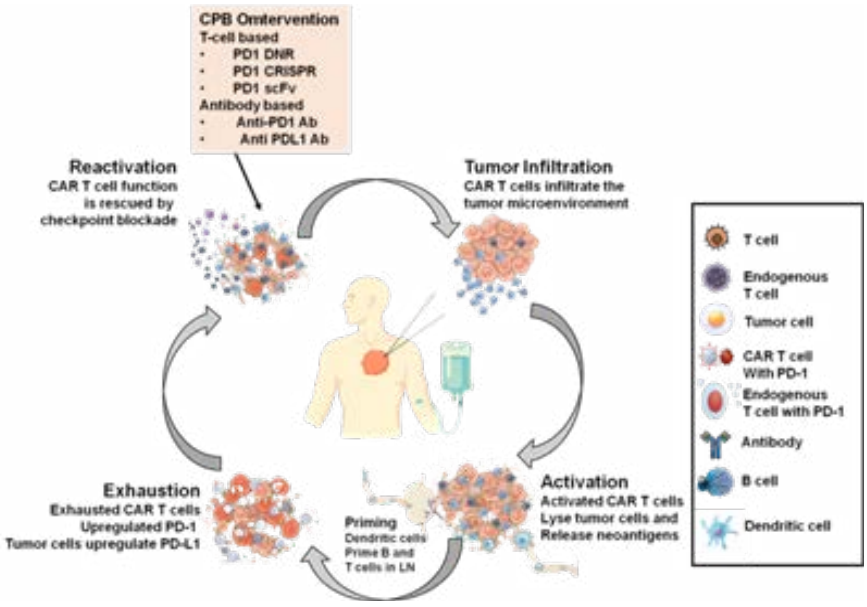

Figure 1. *Checkpoint Blockade Rescues CAR T cell fatigue.*

Table 1. *CAR T cell and Checkpoint Inhibition Therapies in Trials.*

CAR Design/Target	CPB Agent	Prognosis of cancer	Trial	Phase
iC9-GD2 (GD2/iC9-GD2-CD28-OX40) T cells	Pembrolizumab	Neuroblastoma	NCT01822652	I
JCAR017	Durvalumab	Lymphoma of several types, including Non-Hodgkin's, Follicular, Diffused Massive B Cell, and Lymphoma	NCT03310619	I/II
Anti-CD19 CARs	Pembrolizumab	Lymphomas with CD19 amplification include mantle cells, follicles, and diffuse large B cells.	NCT02650999	I/II
zeta CD19/CD19CAR-28 T cells	Ipilimumab	Acute lymphocytic leukemia, B cell lymphoma, and persistent lymphocytic leukemia	NCT00586391	I
KTW-C19/CD19	Atezolizumab	Spreading large B cell lymphoma	NCT02926833	I/II
Central memory T cells that are autologous and express CD4+/CD8+, anti-CD19CAR-4-1BB, CD3, and EGFRt JCAR014	Durvalumab	General heterogeneous B cell cancer	NCT02706405	I
CART-EGFRvIII T cells	Pembrolizumab	Glioblastoma	NCT03726515	I

Table 2. *PD-1 dominant negative receptor CAR T cell therapy and CBP using CAR T cells.*

Checkpoint Inhibition drugs with CAR T Cells	Features	CAR T cells with PD-1 dominant negative receptor
Systemic	Potential toxicity	Localized to tumor
Multiple doses of CPB	Potential doses	Single
No	Targeted therapy	Yes
multiple	Antigen responsiveness	Multiple
Limits of antibody penetration	Limits to tumor penetration	Unlikely
cell-extrinsic	Mechanism	Cell-intrinsic

Approval of PD-1/PD-L1 for this application suggests it has the potential to streamline operations. However, this method has potential drawbacks, including the possible toxicity of systemic, untargeted treatment, antibody tumor penetration, and pharmacokinetics are inherently unpredictable, and PD-1 antibody dosing must be repeated often due to their short half-lives. T cell-intrinsic techniques, some of these issues may be resolved by using gene editing to make "CAR T cells" inherently resistant to "PD-1 signaling".

Cell-Intrinsic Techniques.

One possible exception to the need for individual dosage is provided by an intracellular model in Table 2. In addition, the patient would be eligible for constitutive biological therapy that might provide CPB forever. The induction of an "anti-carbonic anhydrase IX CAR and an anti-PD-L1 scFv antibody" in primary human T cells is one strategy that has been investigated. In the tumor microenvironment, "anti-PD-L1" antibodies accumulated and prevented PD-1 signaling. In an "orthotopic model of human renal cell cancer," CAR T cells boosted effector activity while decreasing the expression of inhibitory receptors, including "PD-1," "TIM-3," and "LAG-3." Locally modified CART19 cells that produced an scFv against PD-1 also showed improved outcomes in vivo.

They created a dominant-negative PD-1 receptor by omitting the internal signaling domain while keeping the extracellular one. The antitumoral efficacy of CAR T cells is significantly enhanced by using an "anti-mesothelin CAR with CD28 and CD3z domains to create a PD-1 dominant negative receptor" in experimental models of mesothelioma and lung cancer. The "switch receptor" approach involves generating a phony receptor that, upon "PD-L1 identification," provides costimulation by combining the "transmembrane and intracellular domains of CD28 with the extracellular domain of PD-1." Anti-mesothelin CAR T cells have greater effector capacities and durability in vivo when co-expressed with a PD-1:CD28 illusion, resulting in long-term effectiveness and complete regression of preexisting tumors. In clinical trials, we want to compare a CAR targeting mesothelin to a "PD-1 dominant negative receptor" since the evidence shows these two approaches are equally effective.

Research is using genome-editing tools like "CRISPR/Cas9" and "TALEN" to disable the “PD-1 signaling pathway”. Tumors are more easily eliminated in vivo and in vitro thanks to “PD-1 deletion CAR T cells”. To develop worldwide "CAR T cells" with improved in vivo effector function and resistance to "PD-1 signaling”, we employed "CAR expression and multiplex genome editing at three loci. Blocking all PD-1 signaling" may paradoxically cause T cells to become permanently specialized and tired in a mouse model of persistent viral infection. T cells may benefit most from upregulating a low level of PD-1, which either cell-intrinsic or cell-extrinsic CPB can then inhibit. Genotoxicity caused by PD-1 gene editing or CAR transgene may negatively impact T cell proliferation and effector activity. It is also essential to identify and reduce off-target cleavage.

Because CAR T cells produce scFvs that inhibit PD-1, administering both treatments individually may not be necessary while still attaining effective doses of both in vivo.

"EGFR-positive advanced solid malignancies" such as lung, stomach, and liver tumors are being studied to determine whether PD-1 antibody-secreting CAR T cells may be used to treat them successfully. Genome-editing methods that disable the PD-1 receptor are also used to investigate its role in T cells transplanted from healthy individuals.

The simplicity of the cell-intrinsic approach makes it appealing to drug administration. Instead of requiring multiple administrations, as with the antibody/cell-extrinsic strategy, CPB-enabled T cells can be administered once. Viral vector integration and T cell memory persistence support their long-lasting transgene expression. Considering the constraints, it is uncertain which of the two ways could be the most effective and least harmful. The cell-intrinsic strategy would restrain the activation of the innate T-cell response, potentially leading to the generation of polyclonal antitumor immunity that is well-suited to highly heterogeneous tumors and, as a result, resistant to antigen escape. Avoiding CAR T cell weariness and reviving an endogenous immune response that had been dormant but was recruited by epitope spreading may both need antibody-mediated CPB, the apparent superiority of the cell-intrinsic method in preventing autoimmunity to off-target epitopes.

Vaccines using dendritic cells.

Antigen-presentation cells called DCs 'present' peptides to T cells, which activates them. An effective cancer vaccine may be created ex vivo containing tumor antigens and reinfused into the patient. DC-based immunizations boost the patient's immune response against their tumor and reduce side effects compared to standard therapy. Numerous "cancers, melanoma, acute myeloid leukemia, multiple myeloma, squamous cell carcinoma of the head and neck, and ovarian cancer" have been the focus of DC vaccine-based phase I and II clinical trials. Leukapheresis collects blood depending on the kind of malignancy and the T cells that need to be activated. It cultivates DCs or monocytes in vitro with a particular cocktail of cytokines to stimulate differentiation into mature DCs. DCs may be primed to identify tumor-derived antigens by exposure to antigen peptide, protein, mRNA, or cancer cells/lysate. When vaccination is given, it stimulates the production of “antigen-specific T cells," shown in Figure 2.

Recent clinical research has focused on refining the ex vivo processes used to create the DC vaccine to increase its efficacy. These adjustments are made to lessen the TME's adverse effects shown in Figure 3. The activation and mobilization of DCs, their maturation, dosage, and delivery, and the development of vaccines employing various subtypes of DCs, are all strategies.

DCs can't function properly when the microenvironment is altered by tumor cells, which suppresses the immune system's antitumor response.

- Metabolic stress induced by tumor cells may alter the metabolic profile and functional capabilities of DCs by decreasing TME nutrition and oxygen.
- Restricted antigen expression of tumor cells may modify or conceal their antigens to evade immune system recognition.
- Alarmins that reduce immunity are expressed, such as MMP-2, which blocks DCs from secreting IL-12, blocking the development of Th1 T cells and activating NK cells.
- Myeloid-derived suppressor cells (MDSCs) and T-regulatory (Treg) cells, immune system suppressors that block T cell proliferation, may be directly activated by tumor cells.

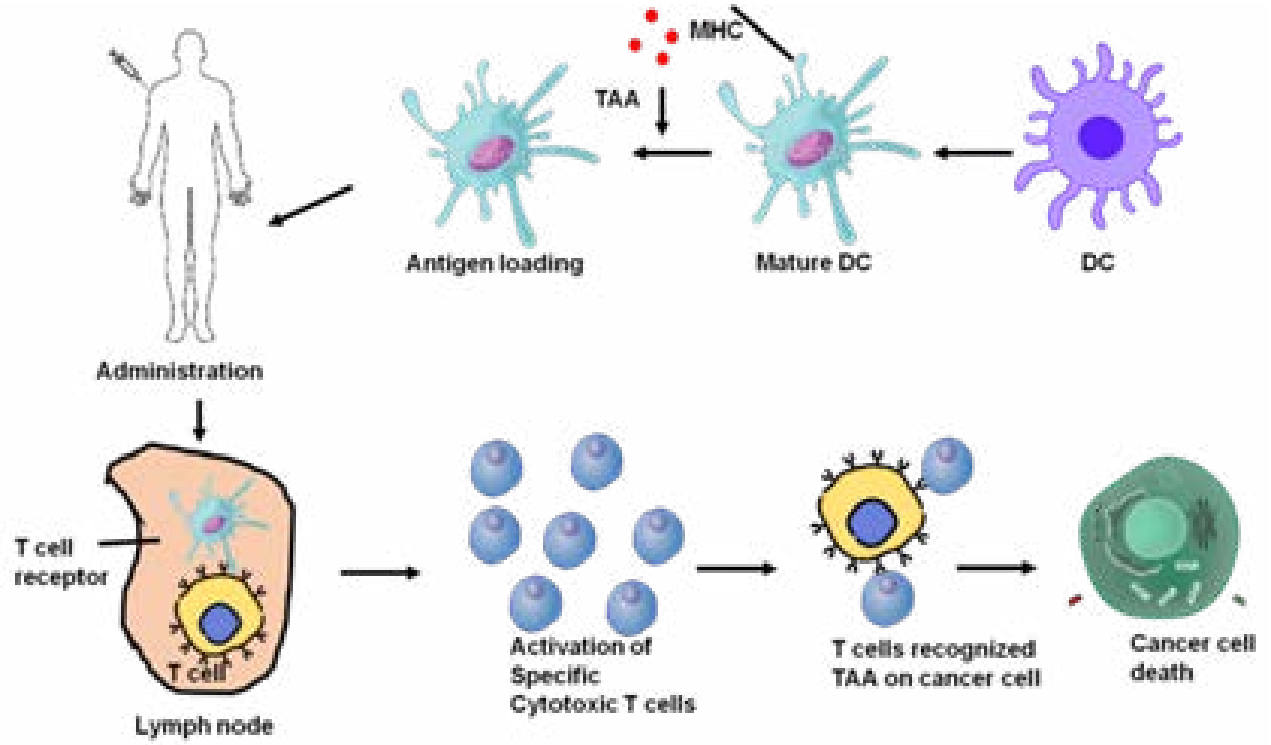

Figure 2. *Human body's response to the DC vaccination.*

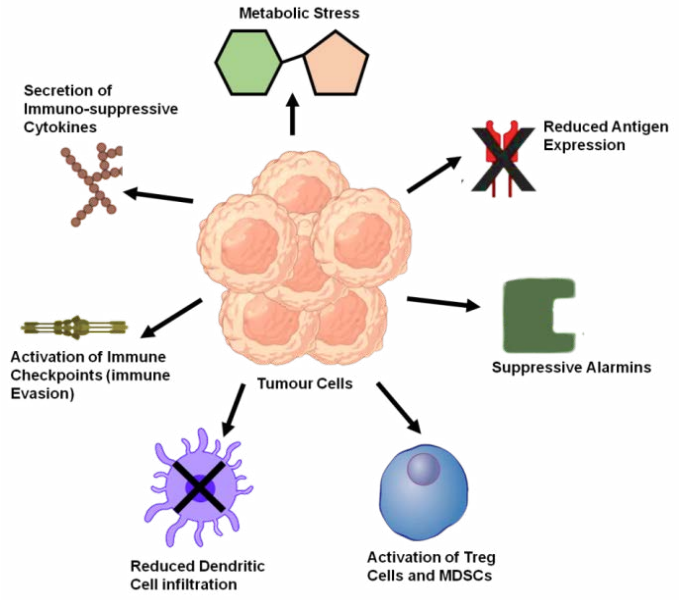

Figure 3. *Cancer-related DC damage.*

- Tumor cells may suppress the production of DC chemoattractants (CC-chemokine ligand 4) to limit dendritic cell infiltration.
- Because tumor cells hide within them, immune checkpoints are triggered. T cell activation may be suppressed by expressing PD-1 and CTLA-4 ligands.
- Immuno-suppressive cytokine secretion of some cytokines (IL-6 and IL-10) hinders DCs from maturing and activating.

Recent Clinical Trials

In this trial, they are testing how well CPB works in tandem with CAR T cells. Different medications, dosages, and schedules are used in this research. No existing models can be used for such an analysis in a preclinical setting. Anti-PD-1 CPB was tested in phase I and phase II trials for patients with malignant pleural mesothelioma who had received mesothelin CAR T cells. 8 of 11 mesothelioma patients who were tracked for at least three months responded to cyclophosphamide preconditioning, a single CAR T cell treatment, and at least three anti-PD-1 doses. Two patients experienced complete metabolic responses. Because tumors exhibited a solid metabolic response even when expressing just 40% of the targeted antigen, the hitherto unknown prospect of neoantigen response and epitope dispersion owing to combination therapy is noteworthy.

Result analysis.

Three different cancer treatments of checkpoint inhibitors, CAR-T cells, and vaccines each combat cancer differently. Each of these therapies has the potential to be successful in the battle against cancer, but the choice of which one to employ will rely on the kind and stage of the patient's particular disease as well as their general health and past medical conditions.

Figure 4 depicts the number of clinical trials in people and children. Cancer treatment symptoms vary by kind, stage, and patient. However, infants, adults, and seniors may experience the following clinical features after cancer treatment. During cancer therapy, kids may endure exhaustion, discomfort, and nausea. They may also have weight, hunger, attitude, and behavior changes. Cancer patients may feel tired, nauseous, vomiting, and lack appetite. They may also feel discomfort, gastrointestinal abnormalities, and mood or sleep problems. They may endure hair loss, skin changes, and sexual dysfunction depending on the malignancy and therapy. Seniors receiving cancer treatment may take weariness, discomfort, and appetite problems.

They may also face consequences from other medical drugs. Seniors are at risk for falls, fractures, and other injuries during cancer treatment. Remembering that cancer therapy may be highly customized and individuals' clinical features and symptoms might differ substantially is vital. Managing cancer symptoms and side effects requires constant collaboration with a healthcare team. Immunotherapy in cancer treatment of adults has the highest number of clinical trials when measured, such as children and seniors.

Figure 5 depicts the multiple phases of cancer patients in clinical trials. Depending on the kind of cancer, its stage, and the particular patient, the clinical characteristics or symptoms of cancer might change. However, in general, phase I and phase II clinical characteristics of cancer may include phase I. The tumor is often tiny and has not yet spread to adjacent tissues or organs in phase I of cancer. Clinical features may thus be weak or nonexistent. The tumor has become more prominent

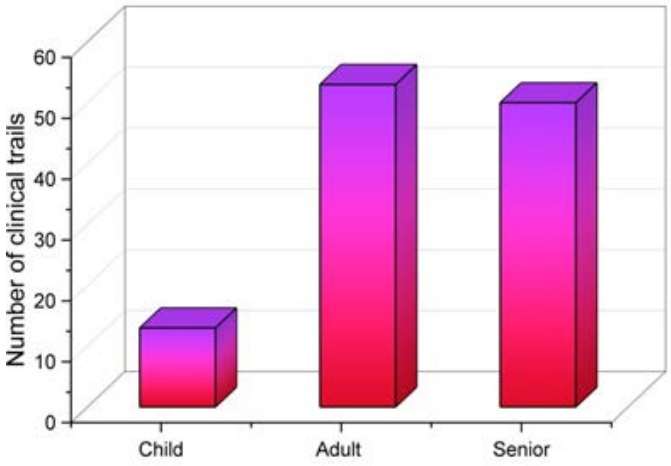

Figure 4. *Number of clinical trials in people and children.*

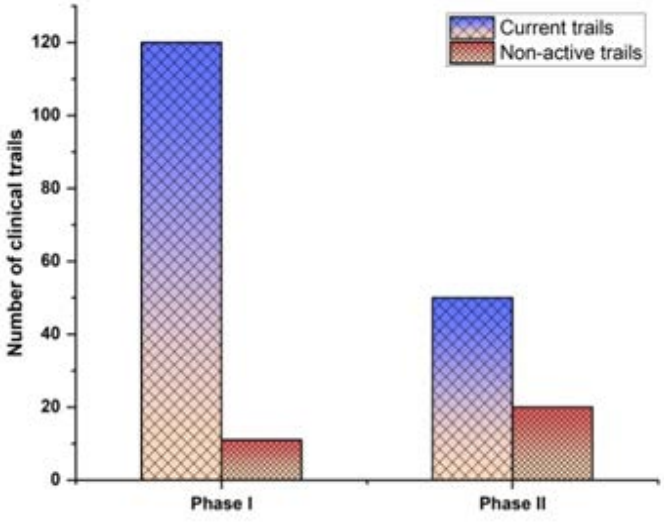

Figure 5. *Multiple phases of cancer patients in clinical trials.*

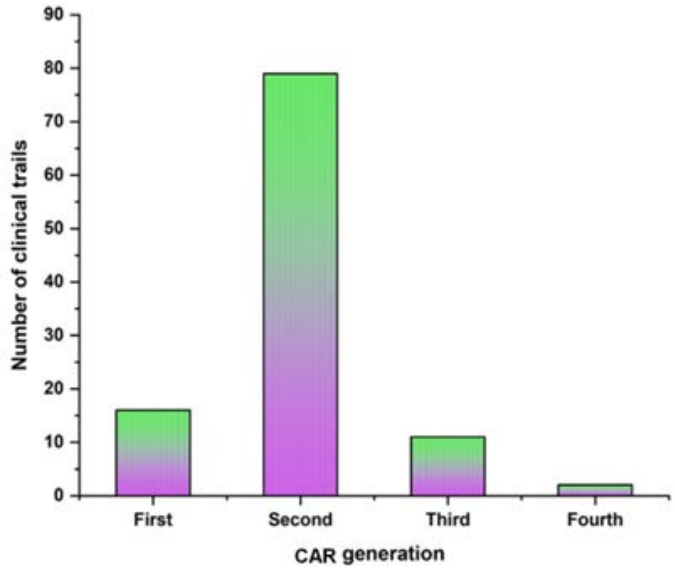

Figure 6. *Number of clinical trials for CAR generation.*

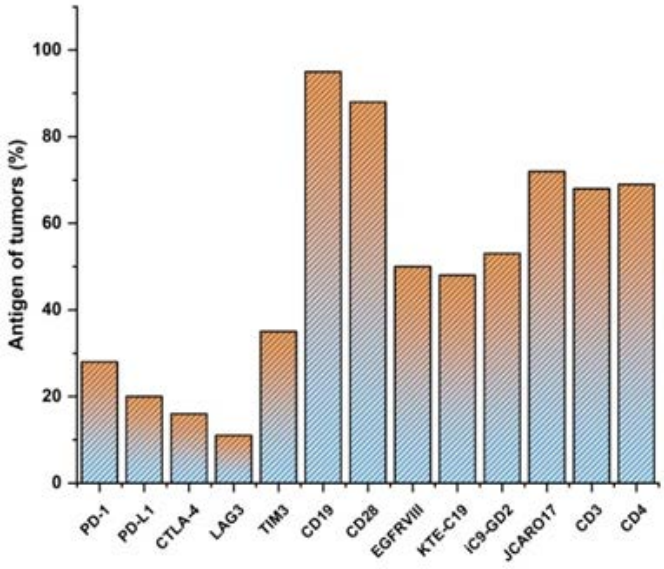

Figure 7. *Antigen of tumors.*

and could have spread to surrounding organs or tissues when the cancer is in phase II. It is crucial to remember that based on the kind and stage of the disease and the specific patient, the clinical characteristics of cancer may vary significantly. Early identification and treatment may enhance results and raise the likelihood of a successful course of action. The immunotherapy in cancer treatment of phase I have the highest number of clinical trials when measured as phase II.

Figure 6 depicts the number of clinical trials for CAR generation. Making “CAR T-cells," programmed to identify and destroy cancer cells, requires genetically altering the patient's immune cells. Making CAR T-cells requires advanced training in genetic engineering and cell culture techniques. Trained professionals and scientists in specialist laboratories often do research like this. However, although CAR T-cell therapy has shown promise in treating several types of cancer, there are still challenges to be overcome, it is still a relatively new and complex procedure, and there may be dangers and adverse consequences. Immunotherapy in cancer treatment of the second generation has the highest number of clinical trials when measured in generations 1, 3, and 4.

Figure 7 depicts the antigen of tumors. The immune system identifies antigens as "foreign" or "non-self" substances. Tumors antigens, which might be proteins or other compounds may be present on the surface of cancer cells or be made by tumors. The immune system may recognize these molecules as "non-self" and actively work to eliminate them. These antigens are unique to cancer cells and are absent in healthy cells. They are the most specific targets for cancer immunotherapies like “CAR-T cell” therapy. The development of more precise cancer treatments is to improve patient outcomes, and researchers must identify and target tumor antigens. However, creating efficient immunotherapies is difficult due to the intricacy of cancer and the diversity of tumor antigens.

Discussion.

Treating early-stage cancers or preventing recurrence tumors using new anticancer vaccinations is helpful since they may increase overall and progression-free survival. Specific inhibitory receptors expressed by T cells, including "TIM-3 and LAG-3", are increased after sustained antigen stimulation and PD-1 inhibition, suggesting that different blocking antibody combinations may enhance function [21]. Cell-intrinsic strategies may be necessary to combat immunosuppression by repeated inhibitory signals, such as administering several checkpoint-targeting antibodies or multicistronic elements that target multiple pathways inside the cell. Involving more innate and adaptive immune system components such as B7-H3, VISTA, and B7S1 may lead to a more potent antitumor response. Several more inhibitory receptors, including B7-H3, VISTA, and B7S1, have been discovered lately and provide new ways to regulate T cell responses [22].

Antigen heterogeneity is one barrier to successful therapy that must be overcome if solid tumors are to be effectively targeted since they are often characterized by diverse antigen expression. Selecting a target antigen that is highly and continuously expressed in tumor tissue is the first step toward resolving this challenge [23]. CAR T cells' antigen-targeting capacity may increase, radiation treatment could be combined (radiation therapy promotes TRAIL-mediated death), or attention might be directed toward antigen-negative tumor cells. T-cell immunotherapy will handle the theory supporting CPB in conjunction with prospective advances in experimental and clinical settings. A prolonged reaction from the effectors is required. More study is needed to determine whether or not CAR T cells are effective, utilizing more accurate and therapeutically relevant models [24]. The group conducting the study looked at the longevity and performance of CAR T cells in malignant pleural effusions to find ways around the present restrictions. On-target off-tumor damage is dangerous since most cars used to treat solid tumors are directed toward antigens in normal tissues. Combination CPB boosts effectiveness but runs the danger of making toxicity worse, as is the case with any functional improvements to focused treatment. Current therapy treatments, such as suppressing CAR T cell generation

with drugs, aren't the only methods to eliminate T cells upon discovery of detrimental effects; suicide genes may be employed to mediate T cell elimination in such cases, although this might be a waste of T cell efficiency [25].

Although antitumor responses have been seen in this current phase-I clinical study, off-tumor intended benefits have not yet manifested. Technology needs dual antigen activation; inhibiting signaling is activated after binding a typical tumor antigen. Using a trans-signaling strategy to dissociate "CD3z signaling" from costimulatory signaling are two methods for increasing the selectivity and decreasing the toxicity of "CAR T cells."

Conclusion.

According to this study, several types of cancer have responded well to anticancer immunotherapy, whether used alone or in combination. The most up-to-date research from this trial shows significant therapeutic benefits for patients with solid tumors. Indirectly, it could eliminate cancer cells by increasing T-cell migration in the tumor microenvironment (TME). Still, therapeutic efficacy may be diminished by resistance mechanisms such as tumor-induced immune evasion. The use of PDL1, LAG3, and TIM3 cell treatments, among others, has shown promise in preclinical examinations of "CAR-T" for the cure of cancer. The optimal dose of chemotherapies, PD1/PDL1 inhibitors, and CTLA-4 inhibitors is still a matter of active investigation. ICI are more likely to be effective in patients who weren't earlier treated with chemotherapy. Future methods to create new ways of researching together and offering these revolutionary medicines for patients, as well as the most information about the treatment of cancerous tumors using CAR T cells and CPB medicines, will be revealed via ongoing clinical studies.

REFERENCES

1. Khan M, Maker AV, Jain S. The evolution of cancer immunotherapy. Vaccines. 2021;9:614.
2. Mi Y, Hagan IV CT, Vincent BG, et al. Emerging nano-/microapproaches for cancer immunotherapy. Advanced Science. 2019;6:1801847.
3. Cheng H, Tai HC. A nanovesicle platform to deliver neoantigens and immune checkpoint inhibitors: To ASPIRE for novel cancer vaccines. MedComm–Biomaterials and Applications. 2022;1:1-3.
4. Igarashi Y, Sasada T. Cancer vaccines: toward the next breakthrough in cancer immunotherapy. Journal of immunology research. 2020;2020:1-13.
5. Alard E, Butnariu AB, Grillo M, et al. Advances in anticancer immunotherapy: Car-T cell, checkpoint inhibitors, dendritic cell vaccines, oncolytic viruses, and emerging cellular and molecular targets. Cancers. 2020;12:1826.
6. Borgeaud M, Kim F, Friedlaender A, et al. The Evolving Role of Immune-Checkpoint Inhibitors in Malignant Pleural Mesothelioma. Journal of Clinical Medicine. 2023;12:1757.
7. Nakajima H, Nakamura T. Towards the era of immune checkpoint inhibitors and personalized cancer immunotherapy. Immunological Medicine. 2021;44:10-15.
8. Schirrmacher V. Cancer vaccines and oncolytic viruses exert profoundly lower side effects in cancer patients than other systemic therapies: A comparative analysis. Biomedicines. 2020;8:61.
9. Zhang ZZ, Wang T, Wang XF, et al. Improving the ability of CAR-T cells to hit solid tumors: Challenges and strategies. Pharmacological research. 2022;175:106036.
10. Lanitis E, Coukos G, Irving M. All systems go: converging synthetic biology and combinatorial treatment for CAR-T cell therapy. Current opinion in biotechnology. 2020;65:75-87.
11. Xue T, Zhao X, Zhao K, et al. Immunotherapy for lung cancer: Focusing on chimeric antigen receptor (CAR)-T cell therapy. Current Problems in Cancer. 2022;46:100791.
12. Shen SH, Woroniecka K, Barbour AB, et al. CAR T cells and checkpoint inhibition for the treatment of glioblastoma. Expert Opinion on Biological Therapy. 2020;20:579-591.
13. Gupta SL, Basu S, Soni V, et al. Immunotherapy: an alternative promising therapeutic approach against cancers. Molecular Biology Reports. 2022;49:9903-13.
14. Al Saber M, Biswas P, Dey D, et al. A comprehensive review of recent advancements in cancer immunotherapy and generation of CAR T cell by CRISPR-Cas9. Processes. 2021;10:16.
15. Yang P, Cao X, Cai H, et al. The exosomes derived from CAR-T cells efficiently target mesothelin and reduce triple-negative breast cancer growth. Cellular immunology. 2021;360:104262.
16. Grosser R, Cherkassky L, Chintala N, et al. Combination immunotherapy with CAR T cells and checkpoint blockade to treat solid tumors. Cancer cell. 2019;36:471-482.
17. Chyuan IT, Chu CL, Hsu PN. Targeting the tumor microenvironment for improving therapeutic effectiveness in cancer immunotherapy: focusing on immune checkpoint inhibitors and combination therapies. Cancers. 2021;13:1188.
18. Watanabe N, McKenna MK, Shaw AR, et al. Clinical CAR-T cell and oncolytic virotherapy for cancer treatment. Molecular Therapy. 2021;29:505-520.
19. Feng M, Zhao Z, Yang M, et al. T-cell-based immunotherapy in colorectal cancer. Cancer letters. 2021;498:201-209.
20. Innao V, Allegra AG, Musolino C, et al. New frontiers about the role of human microbiota in immunotherapy: the immune checkpoint inhibitors and CAR T-cell therapy era. International Journal of Molecular Sciences. 2020;21:8902.
21. Zahm CD, Moseman JE, Delmastro LE, et al. PD-1 and LAG-3 blockade improves antitumor vaccine efficacy. Oncoimmunology. 2021;10:1912892.
22. Chapoval AI, Chapoval SP, Shcherbakova NS, et al. Immune checkpoints of the B7 family. Part 2. Representatives of the B7 family B7-H3, B7-H4, B7-H5, B7-H6, B7-H7, and ILDR2 and their receptors. Russian Journal of Bioorganic Chemistry. 2019;45:321-334.
23. Sun G, Li Z, Rong D, et al. Single-cell RNA sequencing in cancer: Applications, advances, and emerging challenges. Molecular Therapy-Oncolytics. 2021;21:183-206.
24. Panjwani MK, Atherton MJ, MaloneyHuss MA, et al. Establishing a model system for evaluating CAR T cell therapy using dogs with spontaneous diffuse large B cell lymphoma. Oncoimmunology. 2020;9:1676615.
25. Liu B, Zhang W, Zhang H. Development of CAR-T cells for the long-term eradication and surveillance of HIV-1 reservoir. Current Opinion in Virology. 2019;38:21-30.