The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 5792- 5797

Updates in Cancer Immunotherapy: Review Article

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abstract
Background: An adaptable group of cells called the immune system in human's works together to defend the body from external threats like malignant cells. The main types of immunity are natural immunity and immunity that is adaptive. The naturally occurring immune system, which is made up of phagocytes white blood cells, dendritic cells (DC), natural killer cells (NK cells), and circulatory plasma proteins, serves as the body's initial line of defence against pathogens. Utilising the cytotoxicity and antigen-specificity of the human immune system, cancer immunotherapy aims to build an effective anti-tumor immune response that can eradicate all cancer cells without causing damage to healthy tissue.
Objective: This review article aimed to throw light on updates in cancer immunotherapy.
Methods: We searched PubMed, Google Scholar, and Science Direct for relevant articles on Immunity, Cancer immunotherapy and updates. However, only the most recent or thorough study was taken into account between January 2004 and January 2023. The authors also evaluated the value of resources culled from other works in the same genre. Therefore, documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.
Conclusion: Immunotherapy, a precise form of cancer treatment, is becoming more popular. Cancer immunotherapy is probably safer than conventional treatments like surgery, chemotherapy, and radiation because it depends on particular genetic makeup of each patient. The majority of cancer patients have either primary or acquired resistance to immunotherapy medications currently on the market, underlining the demand for novel strategies.
Keywords: Update, Immunity, Cancer immunotherapy.

INTRODUCTION

Immunotherapy aids body to fight cancer, infections, and other disorders by using drugs to either activate or suppress the immune system. Only specific immune system cells are emphasized in some immunotherapies. Some have a more widespread impact on the immune system. Researchers and medical professionals are striving to control immune system to discover and remove tumour cells. These procedures can result in cancer therapy that is efficient [(1)].

The immune system of the human body and cancerous cells normally live in a state of constant balance, and complicated interactions between emerging cancers and the immune system may have an effect on how a disease develops, according to considerable research. Tumours must learn how to avoid detection by immune system to proliferate and metastasize [(2)].

According to the hypothesis of immunological monitoring, immune system has capacity to actively eliminate abnormal cells from body and halt growth of tumour. Elimination, balance, and escape are the three processes that make up the cancer immune editing process. During the process of elimination phase, the body's immune system identifies and eliminates cancerous cells. The human immune system has no ability to completely eradicate all cancer cells during the state of balance stage; some still persist but are not expanding or multiplying. As a result, the mental swinging functions properly are at the state of equilibrium stage [(3)].

Immune system in action

Immune system of human body is a complex and active network of cells that cooperate to protect body from invasion by foreign substances, such as cancerous cells [(4)]. Paul Ehrlich, a physicist who developed side-chain theory of antibody formation, is credited with the discovery that B cells and T lymphocytes provide the highly adaptable adaptive immune system [(5)].

Cancer immunotherapy-precision medicine

After cardiovascular disorders like ischemic heart disease and stroke, cancer is the second most common reason for mortality worldwide. For many cancer patients, the invention and application of localized and systemic therapeutic techniques, such as chemotherapy and radiation therapy, have greatly increased quality of life and survival rates [(6)]. Although systemic chemotherapy and radiation therapy can successfully cure early disease, they may not entirely destroy all malignant cells and may also have unwanted adverse effects due to off-target harm to healthy tissue [(7)].

Utilizing the cytotoxicity and antigen-specificity of human immune system, immunotherapy aims to mount a powerful anti-tumour immune response that is adequate to destroy all tumour cells without endangering healthy tissue. Today's immunotherapies are being created and researched on the basis of advances in knowledge of interactions between human immune system and malignant cells throughout the past century (Figure 1) [(8)].

Received: 26/01/2023
Accepted: 29/03/2023

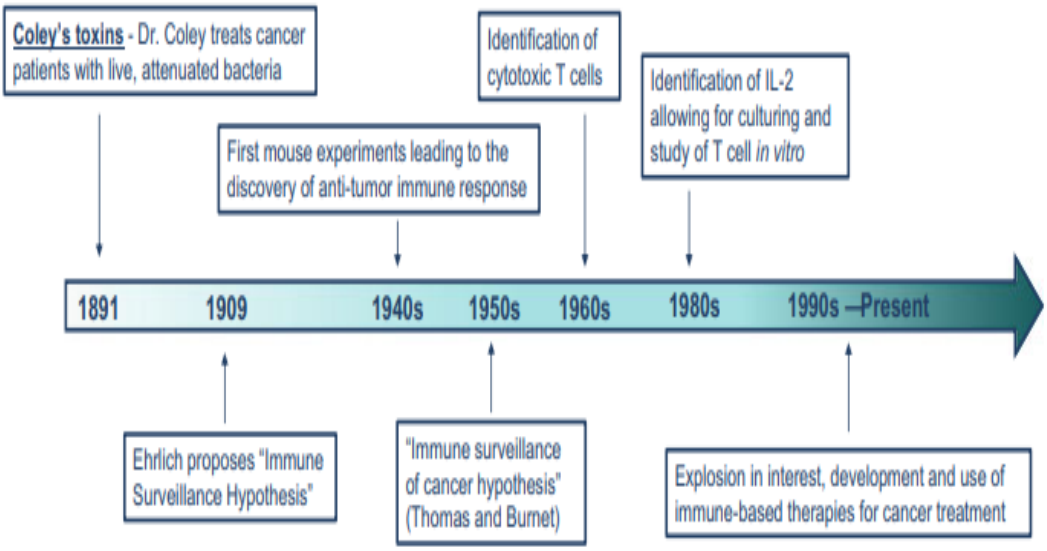

Figure 1: Innovative activities that influenced the development of immunotherapy and immune-oncology in the past [8]

Passive Immunotherapy

Specific antibodies for tumors

Monoclonal Antibodies: Monoclonal antibodies (mAb) constitute some of early immunotherapies studied in clinical trials and authorized for medical purposes because of their increased effectiveness over existing standard of care and adaptability. Opposite to polyclonal antibodies, which were isolated from a pool containing B cells in a living being that had been vaccinated with the antigens and recognise many epitopes inside the exact same antigen, monoclonal antibodies are a single antibody that recognises a single epitope [9].

Antibody-Targeted Radiotherapy:

Although radiotherapy can be targeted to specific areas of known tumours in the body, radiation often results in destruction to neighboring healthy tissue and toxicity-related side effects, which have a substantial influence on quality of life. Improved tumour target delineation with various imaging systems, fractionated dose, and conformal procedures are some of the more contemporary ways to increase the anti-tumour effectiveness of external beam radiation therapy. The technology involves fusing radioisotopes that kill cancer cells after antibody binds to them and internalizes them with tumour antigen-targeting mAbs [10].

Drug-antibody conjugation: Another type of antibody-targeted therapy that has attracted a lot of attention in field of cancer immunotherapy is antibody-drug conjugates (ADCs). A therapeutic mAb and a bioactive cytotoxic substance that is meant to be internally processed by tumour cells and destroy them make up an ADC. Seven ADCs have so far received FDA approval to treat a range of hematologic and solid cancers by targeting tumour antigens such CD33, HER2, CD20, and most recently TROP2 [11].

Bi-specific T cell engagers (BiTEs): Two single-chain attached antibodies make up BiTEs, one of which has been selective to the CD3 domain of the TCR and the other belongs to the relevant neoplasm antigen. Conjugated antibodies provide improved T cell activation and antigen-specific cytotoxic T cell destruction of tumour cells. Blinatumomab, the only BiTE licensed by the FDA, targets CD19 to treat acute lymphoblastic leukemia. Even though blinatumomab significantly increased overall survival relative to chemotherapeutic standard of care, the blinatumomab group's median survival time was still less than 8 months. A number of other BiTEs are now being researched, including an EGFR BiTE in context of non-small cell lung cancer (NSCLC) and a HER2 BiTE when it comes to breast and stomach cancer [12].

Immune checkpoint inhibitors (ICIs)

The selection of specific to an antigen T cells and, ultimately, the T cell repertoire are influenced by the generation of immunologic checkpoints by T cells during the growth of T cells in the thymus. In order to suppress anti-cancer T cell responses, malignant cells also increase immunologic checkpoint proteins and mediators. ICIs are therapeutic antibodies designed to attach to checkpoint receptors or their ligands in a competitive manner in order to prevent their inhibitory action and enhance anticancer T cell responses. The most often targeted checkpoint receptor/ligand combinations are programmed cell death protein 1 (PD-1) binding to programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4) binding to CD80 or CD86 [13].

Adoptive T cell therapies

Adoptive transfer of immune cells, most often T cells having naturally occurring or synthetic TCRs that identify cancer antigens, is a different approach to

passive treatment. Research on mice and people have long demonstrated the significance of T cells in tumour-specific immune responses. It is possible to manufacture huge numbers of T cells with highly specific surface receptors for antigens in a lab setting by genetically editing patient T cells leading to production of very effective therapeutics. Time between peripheral blood collection and the re-infusion of a therapeutic product has been greatly shortened thanks to the optimization of techniques for adoptive T cell product production. To enhance the production of "off the shelf" chimeric antigen receptor (CAR) T and NK cell products for the establishment of immunotherapies for cancer treatment, wherein several genome modification methods have been employed [(14)].

Tumor-infiltrating lymphocytes: Within the TME, immune cells linked to malignancies can behave both pro- and anti-tumorigenic. Tumor-infiltrating lymphocytes (TILs) have been thoroughly investigated for their prognostic importance due to their ability to enter solid tumour environments and increased capability to detect TSA/TAAs due to their intertumoral trafficking. Additionally, these were the original autologous T cells employed in cancer adoptive treatment [(15)].

TCR Transgenic T Cells: Transgenic T cells obtained from patient peripheral blood can be genetically modified to create receptors that can detect TSA/TAAs as an alternative to TIL therapy. Transgenic TCR treatments are created by extracting T cells from a patient's peripheral blood, genetically modifying them to create a TCR specific to a cancer antigen, and then recombining the T cells. After being altered so that only a tiny subset of patient's T cells express therapeutic TCR, the transgenic cells are replicated in vitro to higher numbers before being reinfused into the patient [(16)].

Antigen Selection

A unique TCR on each T cell detects a specific MHC or HLA molecule. A T cell cannot be activated if the appropriate protein antigen provided by the molecules of MHC to which it is assigned is not recognised. Different MHC molecules display different peptide antigens originating from the same protein, depending on the properties of the MHC peptides-binding cleft and the amino acid sequence encoded by the protein [(17)].

Antigenic peptide identification:

It has been demonstrated that, despite the fact that in computational predictive peptide-MHC binding algorithms are frequently utilised as a quick and affordable method of identifying epitopes, these forecast techniques are ineffective at predicting experimentally observed peptides that have elevated affinities for particular MHC molecules. Furthermore, it is necessary for experiments to validate the MHC binding capacity of the proteins selected using in silico approaches. Immunoprecipitation of cell surface using immunoaffinity chromatography and mild acid elution MHC are an alternate method for identifying peptides from cells that are presented with MHC, but this method typically only recovers a small amount of MHC, which leads to inadequate representation of the immunopeptidome [(18)].

T cell extraction and TCR mapping for antigen-specific T cells:

Labelling using peptide-MHC (pMHC) multimer binding and T cell production of cytokines in response to antigen stimuli constitute two of those most widely used techniques to identify antigen-specific T cells. In order to identify T cells that are reacting, pMHC multimers—complexes made up of different amounts of pMHC molecules—are frequently coupled to fluorochromes in flow cytometry. In contrast, the existence of several binding sites in pMHC multimers results in higher TCR binding avidity, which improves the efficiency in antigen-specific T cell identification methods. Individual pMHC interacts briefly and weakly with TCRs [(19)].

Eliminating transgenic—endogenous TCR interactions:

The danger of mismatch matching between therapeutic TCR αβ chains and endogenously produced TCR α and β chains exists when therapeutic TCR sequences are transgenically expressed into otherwise unmodified patient T cells. There is a chance that a particular recombinant and native TCR chain connection could result in TCRs with unanticipated specificities, which could lead to injury that is not intended to be seen and a lack of TAA selection. By switching the regular sections of the human TCR with the ones from the mouse TCR, mismatched coupling was prevented but therapeutic TCR's antigen specificity was preserved. Furthermore, it was proven that introducing cysteine sequences through exact point mutations improves transgenic chain interaction and reduces mismatch bonding with native strands [(20)].

Chimeric antigen receptor T cells:

The CAR, or chimeric antigen receptor, is a different kind of genetically engineered T cell receptor that is now being researched in clinical settings for adoptive T cell treatment. CARs integrate the harmful signaling of a CD8 T cell receptor with the antigen selectivity of a TAA/TSA-specific antibody. The receptor consists of two primary components: (1) The receptor is given antigen specificity by the single-chain variable fragment (scFv), which is made up of the light and heavy variable portions of the tumour antigen-specific antibody. (2) the CD8 T cell receptor's transmembrane and cytoplasmic signaling domain, which, after scFv interaction with tumour antigen, induces cytotoxic T cell effector activities (

Figure 2) [21].

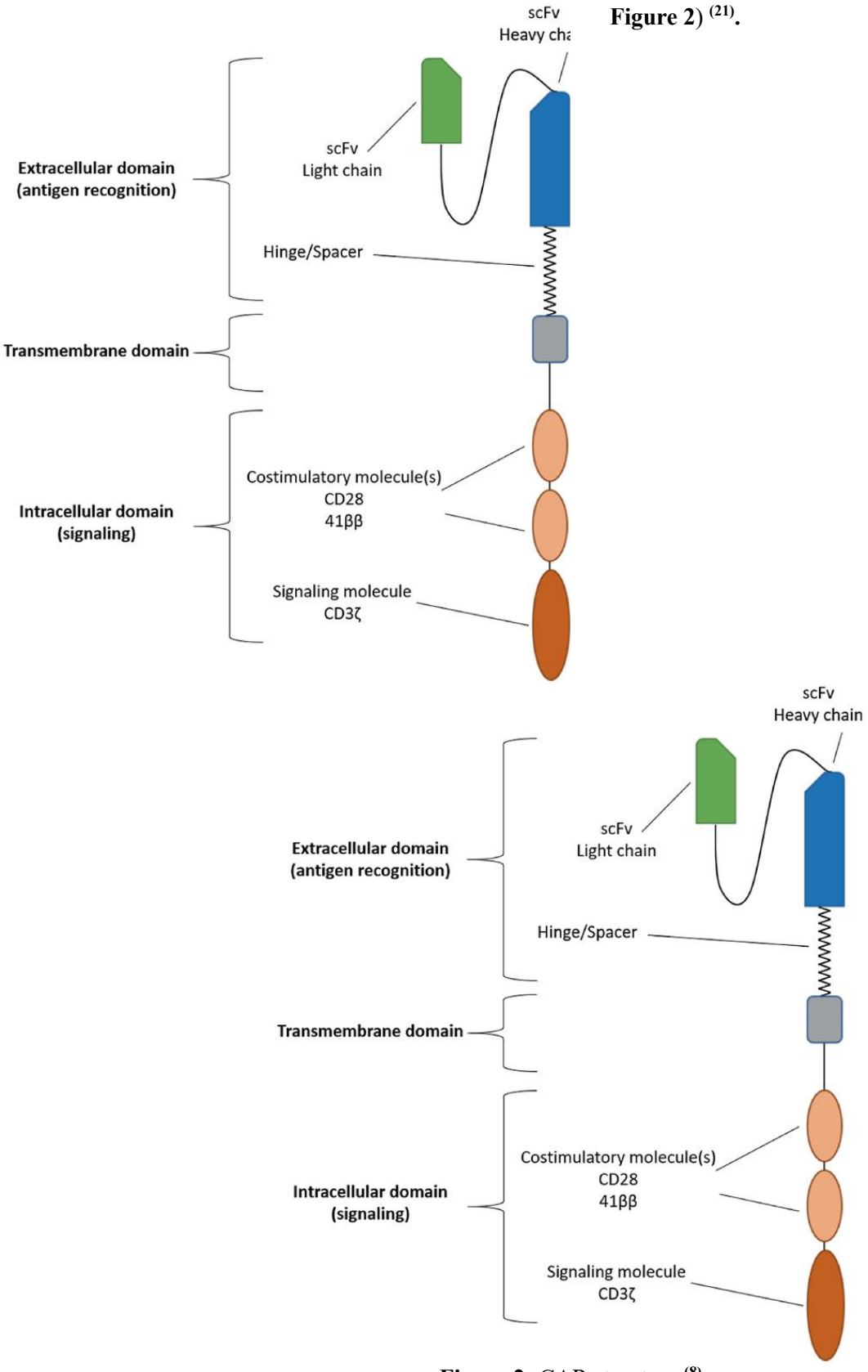

Figure 2: CAR structure [8]

Selecting antigens for CAR T therapy:

The FDA has approved a number of CAR T treatments, all of which are employed to treat B cell cancers. Between 2017 and 2021, three CAR T cell adoptive treatments that target CD19 were authorized, and in 2021, a novel CAR targeting the B cell maturation antigen (BCMA) was authorized to treat multiple myeloma. In clinical trials, all four of the approved CAR T treatments produced remarkable response rates and enhanced patient results. Nevertheless, chronic B cell aplasia and hypogammaglobulinemia in patients are brought on by long-term therapy concentrating on CD19, which is reflected in both healthy and malignant

B cells. This is because healthy B cells are on-target therapeutically eliminated [22].

ScFv antigen affinity

The degree of antigen production in the target cells, co-stimulatory signaling, and total reactivity and operational avidity of CARs are all expected to be influenced by these and other variables. As with TCRs, enhanced antigen recognition and potent T cell responses are usually associated with scFv with a greater affinity for the cognate antigen. High affinity can, however, increase the risk of off-target toxicity. It has been shown that scFv with precisely calibrated antigen affinities can more effectively distinguish between tissues with lower antigen expression in healthy tissue and those with higher densities of TAAs on malignant cells [23].

Optimization of CAR spacer length

The scFv of CARs may encounter more physical barriers as a result of their connection to the T cell appear, which makes it more difficult for the cells to gain and attach antigens. Conversely, despite their intricate or vast three-dimensional frameworks, antibodies may attach to a wider variety of surface antigen conformational epitopes [21]. It has been demonstrated that enhancing the CAR's ability to engage with the targeted antigen involves adjusting the CAR gap length and isotype for a particular scFv. The epitope included in an exogenous antigen on the target cell surface, to which the CAR must adhere, frequently impacts the ideal spacer length. Shorter gaps are frequently sufficient for connecting membrane-distant epitopes with wide exposure, while longer spacers are frequently preferable for binding epitopes that are near the cell membrane or with restricted contact [24].

Selection of T cell costimulatory domains

First-generation CAR constructs included a transmembrane spanning domain, an exterior scFv and hinge, an internal CD3 T cell receptor signaling domain, and a co-receptor, such as CD4 or CD8. These first-generation CARs were unable to use their cytolytic capabilities against certain cancer cells because they lacked T cell costimulatory signals. T cells must receive "signal 1" from the scFv and the intracellular CD3 region attaching to CD4 or CD8 in order to become active and proliferate when exposed to an antigen [25].

Reducing toxicities associated with CAR T therapy

On-tumor toxicity, also known as excessive on-target CAR T activity against tumour cells, and on-target/off-tumor toxicity, also known as CAR T cytotoxic activity against cells that do not express tumour antigens, are two mechanisms that are responsible for the side effects of CAR T therapy. CAR T cells engage the antigen being targeted on cancer cells and activate them, resulting in cytokine release syndrome (CRS), an extensive inflammatory mediators immune system reaction that produces an enormous number of cytokines. Due to immunological activation that is on-target and on-tumor, this is hazardous [26].

Using switch receptors to boost CAR T's efficiency versus solid tumours

To combat the immunosuppressive characteristics of solid tumours, such as existence of immunological checkpoints, which frequently limit CAR T efficacy, novel genetic engineering of CAR constructs is being investigated. With the use of chimeric switching receptors, cells can be activated instead of inactivated when they come into contact with the PD-L1 receptor. The receptors in question pair an internal CD28 T cell costimulatory domain with an external PD-1 domain. With this approach, it has been established that the efficacy of CAR T cells against a variety of preclinical solid cancer types increases [27].

Additionally, it has been demonstrated that the inhibition of TGF-RII's suppressive effects on T cells through the use of dominant-negative TGF-RII improves PSMA-directed CAR T treatments against several animal models of prostate cancer. The usage of a dominant-negative TGF-RII, however, has been demonstrated to induce autoimmune illness and worsen off-target toxicity in mice [28].

Active immunotherapy

Prophylactic cancer vaccines: In at-risk patients, some of the most potent cancer vaccines currently on the market—preventative cancer vaccines based on potent immunisations against infectious pathogens—are administered prophylactically. In order to lower the risk of cancers that can be brought on by certain viruses, these preventative cancer vaccines seek to stimulate a permanent immune system defence against oncoviruses. Typically, these vaccines function by eliciting a potent immune response to antigens created by viruses. Cervarix, Gardasil, and Gardasil-9 to prevent numerous reproductive malignancies and head and neck cancers brought on by human papillomaviruses (HPC), as well as HEPLISAV-B to prevent liver cancer brought on by the hepatitis B virus, have all received FDA approval (HBV) [29].

Therapeutic cancer vaccines: Therapy vaccinations selectively target non-viral TAAs or TSAs in cancer patients, with the goal of inducing a permanent adaptive immune response.

Viral vector-based cancer vaccines: Many virus-based vaccines for cancer have been developed utilising methods used to produce vaccinations for infectious diseases. In order to infiltrate cells with tumour and improve the immune system's defence against the cancer, both dormant (i.e., replication-incompetent) and working properly, replication-competent viruses encoding tumour proteins have been utilized [31].

Cellular-based cancer vaccines: autologous or allogeneic tumor cells: In order to stimulate an immune response to the antigens the tumour expresses, replication-impaired tumour cells or fragments of tumour cells are used when using autologous cancer cells as a therapeutic product. Apoptosis, necrosis, or rendering tumour cells replication-incompetent are the most common methods for killing tumour cells while making whole cancer cell vaccines. Similar strategies have been utilised with hypochlorous acid to create whole-tumor vaccines by inducing the necrosis of cancer cells [(31)].

Dendritic cell vaccines: Specialist APCs recognised for stimulating T cells to respond selectively to antigens include dendritic cells (DC). The use of irradiating autologous tumour cells as a source of cancer antigen for immune stimulation was superseded by DC-based vaccines as the main type of cell-based cancer vaccination under investigation as technological improvements increased researchers' capabilities to analyse and cultivate DC in vitro. All DC lineages originate from the bone marrow's CD34+ hematopoietic progenitor cells [(32)].

Nucleic acid vaccines

An alternate approach that does not include autologous cells is direct immunization with tumour antigen peptides. Utilising genetic data in the shape of RNA or DNA that encodes for tumour antigens proteins or peptides, straight vaccination has additionally been practised. Cells receiving RNA or DNA temporarily express tumour antigens to elicit an immunological response [(33)].

CONCLUSION

Immunotherapy, a precise form of cancer treatment, is becoming more popular. Cancer immunotherapy is probably safer than conventional treatments like surgery, chemotherapy, and radiation because it depends on particular genetic makeup of each patient. The majority of cancer patients have either primary or acquired resistance to immunotherapy medications currently on the market, underlining the demand for novel strategies.

DECLARATIONS

- **Consent for publication:** All authors agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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