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Exploring Oral Immunotherapeutics in Oncology: Uses, Side Effects Novel Approaches, Challenges, and Future Prospects

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Abstract

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Keywords: Cancer, ADCs, Immunotherapeutic, Oral Immunotherapeutic, Combination Therapies, Targeted Therapies, Adverse Effects, Challenges, Advancement in Immunotherapy

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Immunotherapy is a medical intervention in which certain immune system components are used to combat disease. Usually, immunotherapy works by helping the body fight off the offending substance by modifying it as well as boosting the immune system. Biologic therapy or biotherapy are additional terms for certain forms of immunotherapy. Different advances and novel approaches have been studied such as cancer vaccines, immune checkpoint inhibitors, monoclonal antibodies, etc. Oral immunotherapeutics are used in a variety of solid tumors and hematological malignancies but still, these immunotherapeutics have their own limitations and adverse effects. Management of these side effects and optimization of therapeutic benefits remains a challenge. Moreover, challenges such as patient selection, dose optimization, and medication resistance are major issues that hinder the widespread use of oral immunotherapeutics. However, the future of oral immunotherapy in oncology seems to be promising due to the new advancements and research done.

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Introduction

The multistep process known as "human tumor pathogenesis" is what causes cancer cells to transform into tumorigenic and finally cancerous cells. The capacity to keep proliferative signaling going, avoid growth inhibitors, resist cell death, allow for the immortality of replication, promote angiogenesis, start the invasion process, and cause metastasis are a few things included in the multistep process (Karmakar et al., 2021) The immune system of a person's body significantly contributes to controlling tumor growth. Cancers could proliferate, disseminate, and evade the immune system. Cancerous cells and the immune system frequently coexist in a certain dynamic balance. The interaction between cancer and a person's immune system may dictate how a disease develops. In order to multiply and spread, tumors need to learn how to

elude the immune system. In line with the immune surveillance theory, the immune system can actively get rid of aberrant cells and stop the body from developing cancer. Research has indicated that those with impaired or suppressed immune systems are more vulnerable to cancer. Furthermore, although it is debatable, using immunosuppressive medications has been linked to a higher risk of developing several malignancies. It is evident that TILs, or tumor-infiltrating lymphocytes, are frequently linked to increased overall survival indicating that certain tumors' growth can definitely be regulated by the adaptive immune system reaction. But when tumors grow larger, the immune system becomes less and less effective. The goal of immunotherapy is to generate long-lasting tumor decrease by leveraging the specificity and persistent memory of the immune system's adaptive response and maybe even a treatment, albeit only a tiny percentage of patients have been successful in this regard thus far. (Disis, 2014)

Two German doctors named Fehleisen and Busch initiated an initial effort at immunotherapy in the late 1800s when they saw a notable reduction in tumor size following an erysipelas infection. In the following years, immunotherapy was studied in detail by William B. Coley, who executed experiments, studies, and research in which patients with incurable bone cancers were injected with live bacteria, S. pyogenes and S. marcescens(Vasileiou et al., 2023). He used bacteria as an immune stimulant to cure cancer. Nevertheless, because of its poor clinical efficacy, there hasn't been much enthusiasm for cancer immunotherapy. The tumor cells' capacity to evade immune system detection and destruction, which permits them to proliferate within the host, was the cause of their restricted effectiveness. However, a great deal of progress has recently been made in our knowledge of the mechanisms by which cancer cells elude the immune system and the dynamics of interactions that occur between T cells and the target cells. These studies' discoveries provided fresh approaches to preventing cancer's immune evasion in favor of eradicating cancer cells. (Karmakar et al., 2021)

These days, immunotherapy is acknowledged as the fourth cornerstone of cancer care, along with surgery, radiation therapy, and traditional chemotherapy. Immunotherapy has received a lot of attention in the last ten years, in part because studies have shown that it regularly increases overall survival in a portion of cancer patients who have previously been refractory to treatment and would otherwise have a dismal prognosis (Karmakar et al., 2021)

Basic Concepts

The two primary parts of the immune system are intrinsic (nonspecific) immunity and adapted (specific) immunity. The leading advocates of the adaptive immune response are band T-cells. There are three main ways in which the immune system prevents tumors. Initially, by eradicating or decreasing viral infections, the immune system can shield the host against viral oncogenesis. Second, the immune system eliminates infections and inflammation caused by pathogens in a timely manner, hence disrupting the pro-inflammatory microenvironment that promotes tumor development. Third, depending on the expression of tumor-specific antigens, the defense mechanism of a body is able to precisely detect and eradicate different tumor cells; this is fundamentally a function of cancer immune surveillance. Through the development of aberrant surface protein profiles, the immune system distinguishes between precancerous and cancerous tumors during this process. It eliminates them by a number of mechanisms, including the expulsion of cytokines and connected immune cells. Tumors can still develop and go undetected despite all of these precautions, especially if there is a slight immune system deficit. (Karmakar et al., 2021)

New Developments in Immunotherapy:

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are among the most promising kinds of cancer immunotherapy (ICI). Over the past ten years, the FDA has approved several medications for more than nine different forms of cancer. (Dobosz & Dzieci□tkowski, 2019) The fundamental tenet of ICI therapy is that T cells have developed negative regulatory signals, which serve as "checkpoints" to regulate activation. (Waldman et al., 2020) Programmed cellular death 1 and inhibitory receptor cytotoxic T lymphocyte antigen 4 are upregulated by way of T lymphocytes early after stimulation. These molecules attach to co-stimulatory ligands. Cancer cells, myeloid cells, and antigen-presenting cells produce ligands that prevent cytotoxic T cells from becoming activated, which suppresses the defense system and advances cancer development. ICI therapy releases inhibition, inflicting primed and activated cytotoxic T cells to assault and kill most cancer cells. ICI has led to effective treatment of numerous malignancies that are resistant to treatment(Disis, 2014). Immune checkpoints primarily protect organs from damage especially when one's immune system responds to infections They do it by maintaining sensitivity to self-antigens (i.e., preventing

autoimmunity). Blocking T-cell activation and effector activity is the main way to achieve this. There is mounting evidence that one of the primary ways tumors evade the immune system is through immune checkpoint engagement. This has prompted the creation of several cutting-edge drugs that alter immunological checkpoints. (Disis, 2014)

Adoptive T Cell Therapies

Tumor-infiltrating lymphocyte treatment and chimeric antigen receptor T cell therapy are the two forms of adoptive T cell therapies. Below is a discussion of each of these.

CAR T-Cell Therapy

Adoptive cell immunotherapy includes CART-cell treatment (chimeric antigen receptor T-cell therapy). This "permits practitioners to genetically manipulate patient' immune system cells to identify and target tumor cells within the body," as ASCO President Bruce E. Johnson puts it. Patients with refractory or resistant hematologic malignancies experience increased rates of therapeutic response when their T cells are modified to express CARs. In solid tumors, they have shown early signs of clinical action. Significant and particular difficulties arise in the production of CAR T-cell treatments. Though these cells have only recently been employed in clinical settings, the idea behind them dates back to the 1890s, when researchers realized how much an individual's own immune cells could do. (Karmakar et al., 2021)

Depending on the kind of chimeric antigen receptor, there are many generations of Chimeric antigen receptor T cell therapy. The receptor in first-generation CAR is composed of the antibody's single chain variable fragment (scFv), which is directed against the tumor-specific antigen as well as against immunoreceptor tyrosine-based activating motif. (Karmakar et al., 2021). When a particular target antigen recognized by the svFC was delivered to T cells, these first-generation CARs enabled HLA-independent T cell activation. The introduction of costimulatory domains (usually CD28 or 4-1BB) into the CAR design in 2011 resulted in a considerable boost in CAR T-cell proliferation, persistence, and pre-clinical effectiveness (Peterson et al., 2022)Two or one co-stimulatory molecules are introduced to second- and third-generation CARs, respectively (Karmakar et al., 2021) In the end, these "2nd generation" CAR designs have shown unheard-of clinical success, especially when directed against multiple myeloma that expresses against B-cell maturation antigen and against B-cell lymphomas and leukemias that expresses CD19 (Peterson et al., 2022). In the fourth and fifth generations, an IL-2 β-receptor domain or an interleukin (IL)-12 inducer is added to the single co-stimulatory molecule, correspondingly. Checkpoint inhibitor-based immunotherapies have already shown to be promising. Through the genetic modification of T cells, CAR-based immunotherapies enhance the way the immune system reacts to a specific tumor antigen, thereby elevating immunotherapy to another level. Even though protocols and procedures for producing clinical-grade CAR T cells have been established, CAR cell therapies have been applied to a limited number of patients thus far. In order to maintain manufacturing efficiency without sacrificing the integrity and efficacy of the finished product, this cutting-edge technique must be rigorously assessed before being expanded to treat more patients with a wider range of cancer types and at more centers. (Karmakar et al., 2021)

Tumor-Infiltrating Lymphocyte Therapy

In TIL treatment, TILs are amplified with a cytokine cocktail for a few weeks ex vivo in a sterile environment to excite the T cells and produce an adequate number of tumor-reactive T cells. TILs are obtained from solid tumors through surgery. The time needed to produce enough TILs to regulate therapeutic responses and the need for GMP facilities are two major drawbacks of TIL therapy. This could be the reason why TIL treatment has little anticancer impact on many people. In addition, it is challenging for the sickest patients and for those whose needs are more urgent to have them wait for TIL infusion when they have refractory disease. (Karmakar et al., 2021)

Monoclonal Antibodies

Immunological system developed in a lab We call proteins monoclonal antibodies. Antibodies, which the body naturally generates, help the immune system recognize and get rid of invaders including bacteria and viruses. Similar to the antibodies your body makes naturally, monoclonal antibodies are highly specialized target-recognizing antibodies. Certain monoclonal antibodies are also referred to as immunotherapy since they activate the immune system to combat cancer. Several monoclonal antibodies, for example, label cancer cells to aid the immune system in more accurately identifying and eliminating tumor cells. With the help of immune cells, T cells can approach and destroy malignant cells thanks to additional monoclonal antibodies. Thanks to extra monoclonal antibodies, T cells may reach and kill cancerous cells with the aid of immune cells. This process

brings the leukemia cells sufficiently near for the T cells to attack and destroy them. (National Cancer Institute, 2019)

Approved Oral Immunotherapeutics for Cancer Treatment

Over the past 25 years, authorities have authorized 17 immunological medicines based on their anticancer potential when administered either alone or in combination with chemotherapy. .. Many solid tumors, including those of the breast, lung, colon, prostate, skin, kidney, bladder, and head and neck areas, as well as many B- and T-cell cancers, are still often treated with all of these drugs.

The Monoclonal Antibodies

There are now several MABs available to treat cancer. Certain types of cancer can only be treated by those with licenses. Still, others have the potential to combat many cancer forms. Clinical studies are still being conducted on some of the more recent varieties.

Alemtuzumab

Alemtuzumab's long-term efficacy without the requirement for continuous injection and a favorable risk-benefit balance make it approved for the treatment of RRMS. Since both inflammatory and neurodegenerative processes play a role in the intricate etiology of multiple sclerosis (MS), it is critical to continuously monitor the disease's course as it might result in permanent impairment (Hu et al., 2009) Alemtuzumab improves disability and disease relapse rates when administered for RRMS. Alemtuzumab is therefore best suited for patients who have relapsed. When it comes to treating RRMS, there are now dozens of different preparations on the market, each with a unique mechanism of action, efficacy, safety profile, and mode of transmission. (Turner et al., 2013) Alemtuzumab affects MS patients in a variety of ways, including both positive and negative autoimmune side effects; however, it is still unclear if this drug is better suited for use as a first-line treatment than other DMTs. Alemtuzumab is not the first-line treatment, but despite having a high-risk safety profile, it nevertheless offers a respectable therapeutic choice because of its affordability, unique dose schedule, and extended duration of action. Good patient education and adverse effect monitoring may help identify autoimmune diseases linked to alemtuzumab and start early management of them. Alemtuzumab reduces the number of B and T cells in the bloodstream by inhibiting their production of CD52 ligand, which is more abundant in these types of cells than in natural killer cells and other innate immune cells. (Klotz et al., 2012) As a result, the inflammatory impacts of flowing B and T cells are reduced. Alemtuzumab treatment will cause memory and regulatory B and T cells to repopulate and the immune system to return to balance after three to twelve months. (Baker et al., 2017)

Panitumumab

A monoclonal antibody that is entirely human and inhibits epidermal growth factor receptors is called panitumumab. Currently, this drug is authorized for use as a monotherapy in patients who are chemorefractory as well as in conjunction with chemotherapy in first- and second-line cases. Cohen, R. B. (2003)Anti-EGFR drugs are resistant to RAS gene mutations; therefore, panitumumab can only be used to treat RAS wild-type (WT) tumors. (Kim & Grothey, 2008)

Figure 1

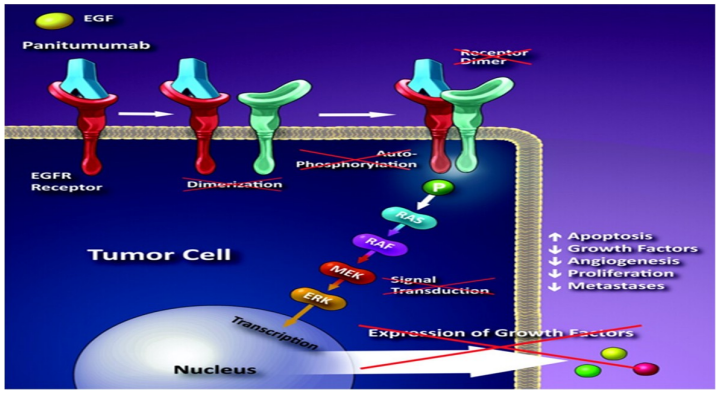

Table 1

No.	DRUG	Brand Name	Receptor	Use
1.	Pembrolizumab	Keytruda	PD-1	Multiple cancer types (Bladder, colorectal, head & neck cancer)
2.	Nivolumab	Opdivo	PD-1	Hodgkin lymphoma
3.	Atezolizumab & Avelumab	Tecentriq Bavencio	PD-L1	Bladder cancer & urothelial carcinoma
4.	Enfortumab vidotin-ejfv & Erdafitinib	Padcev Balversa	FGFR	Bladder cancer and urothelial cancer
5.	Bevacizumab	Avastin	VEGF	Colorectal & kidney cancer
6.	Everolimus	Afinitor	HER-2	Breast cancer & renal cell carcinoma
7.	Dabrafenib & Trametinib	Tafinlar Mekinist	BRAF	Melanoma & non-small lung cancer

Immunotoxins

In order to kill target cells, immunotoxins—bifunctional molecules with both an antibody and a toxic effect—use intracellular toxin action. The binding characteristics of the selected antibody determine the target specificity. Mostly, though not only, immunotoxins are designed specifically to destroy cancer cells as a component of cutting-edge therapeutic strategies (Yamaizumi et al., 1978)

Immunotoxins have additional uses in the management of viral or parasitic illnesses as well as immune regulation. Here, we talk about the effectiveness of using antibodies in combination with protein toxins to target cancerous or tumor cells. Lastly, a great deal has been discovered regarding toxin action and intracellular pathways, even though the main goals are concentrated on the creation of innovative cancer cures. Toxins are therefore regarded as both biological probes and medications for treating human illness (Thorpe et al., 1978)

Novel Approaches in Immunotherapy

These days, immunotherapy is a fantastic and long-lasting form of cure for cancer therapy. Meaningful advancements have been achieved in grasping the tangled interactions among antigen-presenting cells, cytotoxic T lymphocytes, and tumor cells. Soon, the focus will be on exploring rational combination therapies involving checkpoint inhibitors alongside immune agonists, chemotherapy, radiotherapy, or antiangiogenic agents. Ongoing trials are researching optimal timing for administering these agents, whether in the adjuvant setting when tumor burden is minimal or in the frontline setting for metastatic disease.

Adding Omalizumab

Studies indicate that pre-treatment with omalizumab may amplify the efficacy and safety of SCIT, enabling more patients to progress to maintenance therapy. Despite these positive outcomes, uncertainties persist regarding the optimal duration of treatment and the feasibility of safely discontinuing omalizumab after achieving maintenance immunotherapy (Jones et al., 2021).

TLR-4 Agonists

There are approximately 13 TLR ligands in humans, with 11 already identified. Recent studies have demonstrated that preseasonal injections of this agonist can reduce symptoms, decrease medication usage, elevate antigen-specific immunoglobulin (Ig)G levels, and mitigate the seasonal rise in IgE (Brown et al., 2020).

CpG Molecules: TLR-9 Agonists

CpG molecules, acting as TLR-9 agonists, have garnered attention in the past. Despite the discontinuation of a promising candidate, Tolamba, due to clinical study issues,

Cytos Pharmaceuticals has introduced a novel approach. By encapsulating a CpG molecule within a virus-like particle (Green et al., 2019).

Depigoids and Recombinant Peptides

Innovative approaches like demigods, which involve modifying allergens into pure allergoids or polymerized forms, have shown promise in blunting allergic responses. Additionally, the development of recombinant peptides devoid of B-cell epitopes offers a safer and universally applicable alternative for various allergies (Black et al., 2020).

As our understanding of the immune system's biology improves, numerous novel targets are expected to be investigated in clinical trials. Emerging checkpoints like TIM-3, BTLA, VISTA, CD160, and CD244 are gaining attention, with Phase I trials underway for CCR4 agonists in combination therapies.

Cancer Vaccines

Peptide Vaccines

These vaccines target specific tumor antigens like MAGE-A3 and MUC-1 and have shown mixed results in clinical trials. While trials targeting MAGE-A3 in melanoma and non-small cell lung cancer did not demonstrate significant benefits, telemovie (L-BLP25) targeting MUC-1 in unresectable stage III NSCLC also did not improve overall survival. Rindopepimut, an EGFRvIII peptide, showed promise in relapsed glioblastoma with improved 12-month overall survival rates.

Tumor Cell Vaccines

In a phase III study, belagenpumatucel-L, a heterologous tumor cell vaccination for non-small cell lung cancer, did not demonstrate better overall survival when compared to a placebo. It is made up of TGF-β2 antisense gene plasmid-modified irradiation NSCLC cell lines.

Immune Cell Vaccines

Sipuleucel-T (Provenge) has been successful in prostate cancer by co-culturing autologously harvested PBMCs with PA2024, resulting in improved overall survival in metastatic castration-resistant prostate cancer patients

Comparing Oral and Intravenous Immunotherapy

The usage of immunotherapy in the treatment as well as management of cancer has garnered significant attention in these years, with research being done on both oral and intravenous (IV) delivery systems. Checkpoint inhibitors, one type of oral immunotherapy, have the benefit of being easy for patients to take and may result in greater compliance (Ribas & Wolchok, 2018). However, Intestinal absorption, first-pass metabolism, and medication interactions can all have an impact on the bioavailability of medications taken orally (Hanley et al., 2020).

In comparison to oral administration of immunotherapeutic agents, intravenous administration provides two advantages of intravenous injection increased concentration at the tumor site and direct drug transfer to the systemic circulation. (Pardoll, 2012). Additionally, IV infusion may need more frequent trips to medical centers, which might be costly and unpleasant for patients. However, intravenous (IV) delivery offers better control over the drug's pharmacokinetics and guarantees that the whole intended dosage reaches the target tissues. (Postow et al., 2018).

Both these types of therapies have been associated with different types of side effects that vary from mild to serious. Orally administered drugs cause some gastrointestinal side effects, while IV immunotherapy might result in adverse events relating to the immune system or responses associated with the infusion that impact different organs (Postow et al., 2018). For better effects of immunotherapy proper management and monitoring of side effects associated with it should be done.

The effectiveness and safety of oral and IV topotecan in patients having small-cell lung cancer were compared in one open-label, randomized phase III research. Every 21 days, patients were randomized to receive either IV topotecan 1.5 mg/m2/d on days 1–5, or oral topotecan 2.3 mg/m2/d on the same days. The response rate served as the main benchmark. The response rates showed no statistically significant variation between oral topotecan (18.3%) and IV topotecan (21.9%) in the intent-to-treat study. The two groups' 1- and 2-year survival rates, as well as their median survival times, were comparable.

With such a goal, both oral and IV immunotherapy as treatment began with the hopes of activating anti-tumor immunity, which again highlights the importance of application selection, combining factors such as patient preference, tumor feature, drug pharmacokinetics, and/or side effects, etc. Research should be done companionably to discover ways to accentuate these treatments to make them beneficial and effective for every kind of patient in order to analyze the impact of different agents and further improve patients survival with cancer.

Adverse Effects of Oral Immunotherapy

Sublingual Immunotherapy (SLIT) was introduced for the first time in 1986 in a double-blind randomized trial to avoid severe and fatal adverse events (AEs) of subcutaneous immunotherapy (SCIT), more convenient. SLIT adverse reactions (AEs) vary from case to case, with local reactions being the most common. Reports of them are sub-optimal and their descriptions lack uniformity- so it is not possible to compare them with other studies, judge risk factors, or recommend appropriate interventions. The WAO and regional organizations have favored some standard grading systems, especially for local reactions connected with SLIT (in one case to be distinguished between irritation and put into practice local reactions as MSC Directive 65/65 EEC Article 3. 02. 9 provides for clinical pathology-based definitions for SCIT) while there is already aversion on the grading of systemic adverse reactions that should have made a subject of the guideline practice parameters (Coop & Tankersley, 2008)

Challenges Faced in Oral Immunotherapeutics

With a high death rate, cancer—especially oral cancer—is a serious global health concern. The most prevalent kind of oral cancer is called oral squamous cell carcinoma, and risk factors for the disease include drinking alcohol, smoking, and having HPV. Effective therapy depends on an early diagnosis, but current diagnostic techniques, such as biopsy and histological evaluation, have drawbacks**.**

Challenges in Oral Cancer (OC) Diagnosis

Even though it is easy to examine the oral cavity, up to 50% of cases with OC go undiagnosed till the disease has advanced considerably.

Early identification is crucial, as it significantly improves survival rates, with early detection leading to over 90% survival after five years, compared to only 30% for late-stage diagnoses. Unfortunately, the majority of patients—nearly 60%—have advanced diagnoses, which has a negative impact on their prognosis. The main cause of the survival rate stagnation is misdiagnosis.

Challenges in Oral Cancer (OC) Treatment

Treatment for OC typically involves surgery, radiation, chemotherapy, antibody-blocking therapy, or a combination of these approaches. The choice of treatment depends on various factors, including the cancer's location, size, stage, type, progression, and the patient's overall health. However, there are significant limitations to current treatment options. Surgery is often constrained by nearby critical structures, necessitating adjuvant therapies in some cases. Radiation therapy may fail to treat advanced tumors effectively and is limited by toxicity concerns. Chemotherapy is mainly used in combination with radiation therapy and can cause various side effects, particularly in the oral cavity.

Complications in Oral Cancer (OC) Treatment

Chemotherapy and radiation therapy's detrimental effects on healthy oral tissues make patients receiving OC treatment more vulnerable to problems These therapies can hinder the regeneration of healthy cells in the mouth lining, leading to oral problems such as mucositis and infections. Radiation therapy can directly damage bones, salivary glands, and oral tissues, further exacerbating complications. Additionally, the balance of oral bacteria may be disrupted, leading to further oral health issues. Overall, managing these complications is crucial for improving patient outcomes during OC treatment (Umapathy et al., 2023)

Future Prospects:

Reduce Financial Burden

High-priced cancer drugs hurt the public in two distinct manners: initially, they raise the cost of care for patients, insurers, and the state who can afford them; second, they impede the creation of equally effective but less costly alternatives. The need for inexpensive alternatives is particularly important in circumstances where the value of novel medicines is minimal since their cost-effectiveness ratio is typically unfavorable.

Combination Therapies

Combination therapies for repurposing drugs for cancer offer several potential benefits, such as the capacity to combat drug resistance in already available cancer therapies, reduced toxicity, enhanced efficacy, and decreased dosage at a comparable or greater level of efficacy.

Repurposing Drugs

Furthermore, repurposing drugs is a more cost- and time-effective method of increasing the number of readily accessible cancer medicines than de novo creation. Concentrating on creating a limited number of medications that target the key proteins and systems or the most altered protein in cancer is one workable technique to enhance therapy results. This strategy promises more accessible and efficacious cancer therapies

by extending the net to cover a significant portion of cancer cases. Personalized treatment is still a crucial area for research, but the creation of such widely used medication combinations can greatly increase our capacity to enhance cancer patient's quality of life(Weth et al., 2023)

Second, additional study is required to understand the suppressive effect of the TME on ICI as well as alternate checkpoint inhibitor pathways that enable tumor escape in order to develop more potent ICI treatments. Patients with solid tumors as well as a highly immunosuppressive TME have not responded well to CART, however, some patient subgroups with hematologic malignancies have demonstrated encouraging results. It has demonstrated the ability to boost CART and ICI efficacy by concentrating on the TME's immunosuppressive elements, namely TAMs. To find the most promising approaches, clinical studies involving these agents will be needed. It can be an initial step or in tandem with ICI along with CART. It has demonstrated the potential to target components of alternative pathways with ICI, which will probably open the door for new combination therapies. It may finally be possible to achieve better results with novel CART engineering that enables enhanced CART trafficking and decreased immunosuppression within solid tumors. Vaccines against cancer have also advanced significantly in recent years. Studies that combine TME targeting with neoantigen vaccines, in particular, have the potential to expand this fascinating field (Peterson et al., 2022b)

Targeting Therapies

Targeted distribution of biofilm nanomedicine methods to tumor locations with long-acting circulation in blood vessels can successfully preserve the biological activity of immune-related molecules, such as tumor antigens, during CIT.

Targeted modification can also address a number of issues and problems with current CIT strategies. This implies that there is a lot of room for clinical translation. Future research must first perform serial sampling and longitudinal evaluation of fresh human specimens (tumor, blood, serum, and microbiome) during treatment in order to clarify the heterogeneous mechanisms of drug resistance in combination with a thorough analysis of multiple factors; alternatively, novel techniques that include whole-genome sequencing, single-cell sequencing, and epigenetic analysis must be adopted in order to identify the characteristic drug resistance sites or sub-clones.

Advancements in Immunotherapy

Immunotherapy may be used to treat a greater variety of malignancies because of the ongoing, in-depth investigation of resistance mechanisms. Second, with the advent of numerous high-tech technologies, it is important to investigate efficient biomarkers for patient screening according to distinct tumor features and microenvironment phenotypes.

Challenges and future directions

Lastly, multidisciplinary research directions in cancer treatment modes (including surgery, internal medicine, radiation, and drug combinations) are being pursued to create the most customized treatment plans based on the unique needs of each patient. In order to meet these challenges, basic scientists and clinicians working together must conduct basic research. To enhance cancer patients' treatment options and progress CIT, resources must also be allocated towards hastening the knowledge of the complex links between immunity and cancer (Bai et al., 2021).

Conclusion

In conclusion, cancer immunotherapy is broad and is gradually but continually evolving using different novel approaches such as Monoclonal antibodies, Adoptive T cell therapy, Immunotoxins, etc. All these approaches have shown significant clinical outcomes. Approved oral immunotherapeutics have increased the treatment outcomes irrespective of all the side effects associated with them and are used in many solid tumors and malignancies. There are still many challenges associated with oral immunotherapeutics, its dose management, overcoming resistance, etc that need to be worked upon. Exploring alternative checkpoint inhibitor pathways, enhancing CAR T cell therapy efficacy, and advancing cancer vaccines. repurposing existing drugs and developing targeted therapies offer potential solutions to overcome challenges A lot of new studies and research work is been done to overcome the challenges of oral immunotherapeutics. Continued multidisciplinary research efforts and technological advancements will be crucial in harnessing the full potential of cancer immunotherapy and improving outcomes for patients.

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