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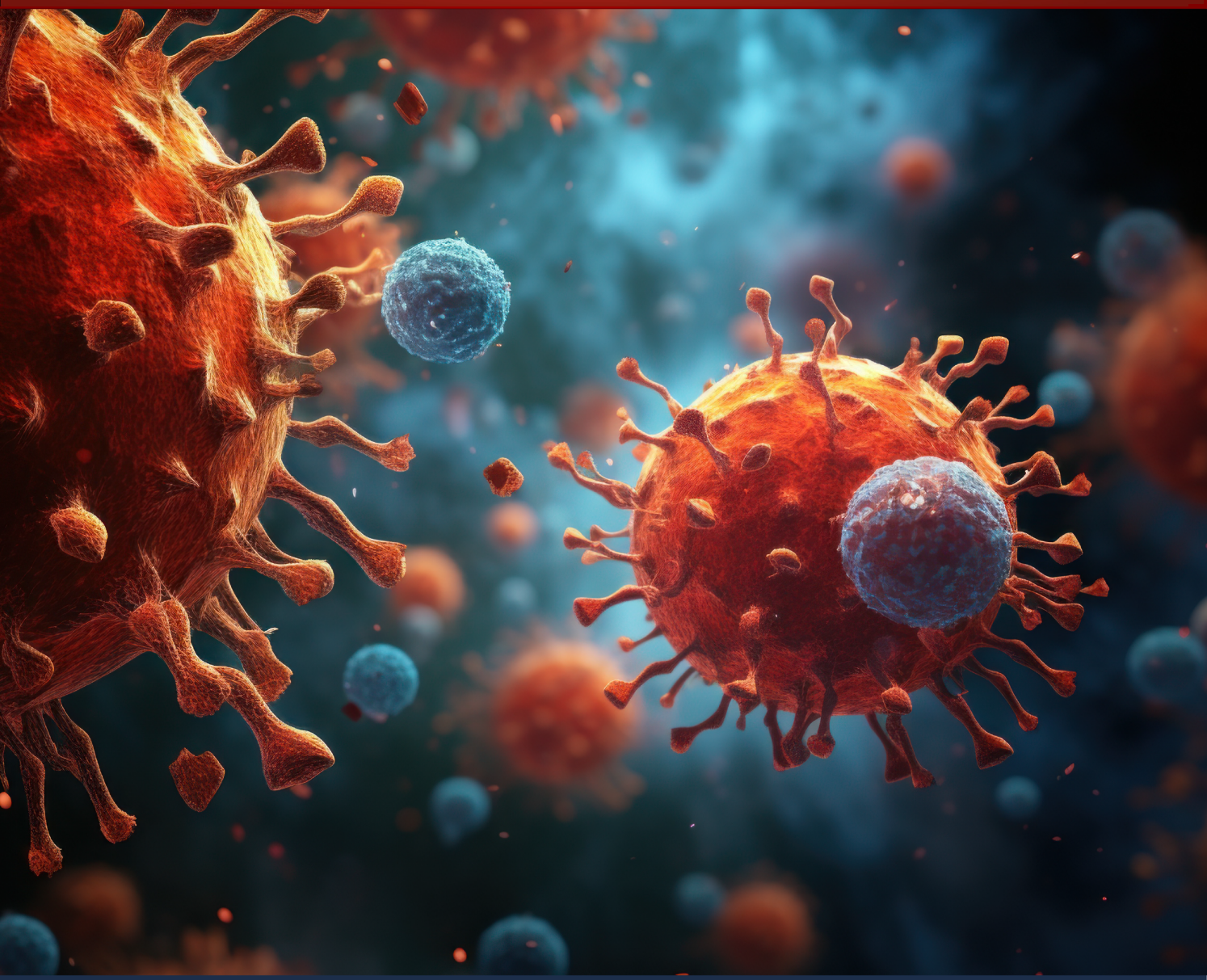

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Immunological Checkpoint Inhibitors Represent a Novel Approach Within the Realm of Cancer Therapy

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Abstract

The advent of immune checkpoint inhibitors (ICIs) has ushered in a new era in the field of cancer therapy, allowing for the potential of prolonged life in patients with metastatic illness, and offering novel therapeutic applications in the early stages of the disease. Immune checkpoint inhibitors may reinstate the immune system's capacity to combat cancer cells and halt their proliferation by obstructing these proteins. The validity of these results is supported by sufficient clinical trial evidence, and now, many immune checkpoint inhibitors have been authorized by the FDA and are available on the market for the treatment of different kinds of malignancies. They work by inhibiting checkpoint proteins such as CTLA-4, PD-1, PD-L1, etc. They may be used alone or in conjunction with other cancer therapies, such as surgery, radiation, or chemotherapy. In this article, we offer a comprehensive review of these inhibitors and their significance as biomarkers, immune-related bad effects, and their relevance in clinical research for the treatment of different types of malignancies. Additionally, we discuss some potential future possibilities.

Keywords: Immune checkpoint inhibitors, Cancer immunotherapy, CTLA-4, PD-1, PD-L1.

Introduction

The immune surveillance of the tumor regulates and monitors the microenvironment via the innate and adaptive immune systems. Antigen-presenting cells play a crucial part in this monitoring process by recognizing and displaying tumor neoantigens to inactive T-cells. Upon exposure to the antigen, naïve T-cells undergo proliferation and activation, therefore initiating an immune response against the tumor. Both stimulatory and inhibitory signaling molecules regulate this process (1). The suppressive signals are sent by immunological checkpoints, including B and T lymphocyte attenuator (BTLA), programmed death protein 1 (PD-1), and cytotoxic T lymphocyte-associated protein 4 (CTLA4) (2). CTLA-4 and PD-1 are present on the surface of T-cells and can inhibit their activation. CTLA-4 is present in regulatory T cells (Treg cells) and assists in immunological suppression. PD-1 is also present on the surface of B cells and other cells involved in immune response (3).

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When PD-1 interacts with its corresponding proteins, it can inhibit the T-cell response. Nevertheless, cancer cells present in the tumor microenvironment can evade the effects of anti-tumor mechanisms by activating these regulatory sites via the amplification of CTLA4 or PD-1/PD-L1 expression. In addition, they endeavor to do this via inhibiting antigen presentation (3).

The excessive expression of these checkpoints on the surface of immune cells may restrict the ability of the immune system to recognize and target cancer cells. This allows the cancer cells to evade examination and proliferate without restraint. It is a frequent occurrence in cancer cells and may serve as a mechanism for developing resistance to immunotherapy. Moreover, the immune system recognizes the distinct proteins or neoantigens produced by genetic changes in cancer cells as alien entities, making them potential targets for the immunological response to cancer (4). Nevertheless, there are instances when the immune system fails to accurately recognize neoantigens as alien, resulting in the cancer cells eluding immune monitoring and proliferating. This may happen when the immune system is weakened by checkpoint proteins, such as CTLA-4 and PD-1/PD-L1 (5). Checkpoint proteins restrict the activity of immune cells by anchoring certain ligands to the outer layer of cancer cells. This connection signals the immune cells to suppress their reaction, enabling the cancer cells to evade immunological assault. Immune checkpoint inhibitors (ICIs) enhance the effectiveness of the immune system in fighting cancer cells by inhibiting checkpoint proteins. Therefore, genetic changes in cancer cells may produce neoantigens that can be targeted for immune-mediated control of tumors (6). Nevertheless, the activity of the immune response could be restricted by checkpoint proteins. By inhibiting these checkpoint proteins with ICIs, it is possible to eradicate cancerous cells and enhance the effectiveness of immunotherapy. These medications may be used to target and inhibit the route of immunological checkpoints that are overexpressed, thus enhancing the ability of the immune system to detect and eliminate uncontrolled proliferating cells (6). This study specifically examines ICIs and their significance in the treatment of cancer. The origins of ICIs in immunotherapy may be traced back to the 1890s. However, its use for cancer treatment specifically began in the 1990s, when scientists first recognized the significance of immune checkpoints in controlling the immune response. The first ICIs for cancer therapy were created in the early 2000s, however, they were officially approved for treating skin cancer only around 2010 (7, 8). Since their introduction, ICIs have played a crucial role in the treatment of cancer and have had a remarkable effect on patient outcomes in several types of cancer, including melanoma, lung tumors, hepatic carcinoma, tumors of the head and neck, ovarian cancer, renal cell tumors, and others. These medications have resulted in enduring therapy responses and even complete remission in cancer patients with advanced-stage disease (9).

Introduction of ICIs

Immune checkpoints are categorized as immune cell surface receptors that regulate the activation or suppression of immunological responses. CPIs are a kind of immunotherapy that enhances the immune response against tumors by blocking the cell surface receptors of T cells (10). This category of immunotherapy has been extensively studied and is now regarded as the most fully researched. It plays a crucial part in the treatment of many types of cancer. Two very effective strategies for inhibiting checkpoints that have gained significant popularity in the last ten years are the blockage of PD-1/PD-L1 and CTLA-4 molecules. Additional targets, including inhibitory receptors such as T-cell immunoglobulin and mucin 3 (Tim-3), V-domain Ig suppressor of T-cell activation (VISTA), lymphocyte activation gene 3 (Lag-3), and activating molecules such as OX40 (CD134) and glucocorticoid-induced TNFR-related protein (GITR), are currently being studied. The identification of T-cell-negative regulation by CTLA-4 served as a catalyst for the adoption of CTLA-4 blockage as a kind of cancer immunotherapy (11). The first research conducted by Allison et al. has shown that inhibiting CTLA-4 in mice effectively halted tumor growth and facilitated the development of immunological memory, enabling the animals to consistently reject the tumor. Due to the positive results in preclinical models, humanized monoclonal antibodies have been developed to block the interaction between CTLA-4 and its ligand (B7) in cancer patients (12). This has led to the initiation of clinical studies. This marked the beginning of a significant change in the area of cancer immunotherapy since it effectively stimulated the immune system to target tumors. The finding by Honjo et al. that the interaction between PD-1 and PD-L1 leads to T-cell fatigue sparked the concept of targeting this process as a novel approach in cancer immunotherapy, warranting more exploration (13). Studies conducted in preclinical models have shown an increase in T-cell activation and interaction when PD-L1 inhibition is applied. Furthermore, the blocking of similar nature in mice tumor models demonstrated an increase in the immune response specific to the tumor cells and resulted in the regression of the tumor. The positive outcomes shown in preclinical research regarding PD-1/PD-L1 suppression have stimulated the creation of several

humanized antibodies and the initiation of clinical trials in individuals with advanced malignancies. The many classifications of these antibodies and their specific uses are further elaborated upon in the subsequent sections (13).

T cell CPIs

CTLA-4

CTLA-4 is a molecule that acts as an inhibitory checkpoint and is found in high levels on both activated T cells and Tregs. Dr. James Allison's groundbreaking preclinical research showed that CTLA-4, a molecule similar to CD28 but with a stronger binding to B7 ligands, effectively blocks T-cell proliferation and the generation of IL-2 by outperforming CD28 binding (14). CTLA-4 expression is triggered during T cell activation and limits the excessive growth of activated T cells. Significantly, the obstruction of CTLA-4 interaction by using an anti-CTLA-4 antibody to hinder the "switch-off signals" in T cells resulted in long-lasting T cell-mediated anti-tumor immune responses and tumor regression in mouse models (15). Following preclinical investigations, it was shown that the enhancement of tumor rejection caused by anti-CTLA-4 was due to an augmentation in effector CD4 and CD8 T cells, accompanied by a reduction in Tregs. Importantly, the effectiveness of anti-CTLA-4 treatment was not restricted to only one kind of tumor. Multiple studies done on various mouse tumor models showed that anti-CTLA-4 therapy had wide-ranging effectiveness. The effectiveness of ipilimumab, a human monoclonal anti-CTLA-4 antibody, was evaluated in clinical studies. The results demonstrated significant clinical effectiveness, leading to its approval by the Food and Drug Administration (FDA) for the treatment of melanoma in 2011 (16). Significantly, a cohort of patients diagnosed with advanced melanoma who had this treatment exhibited enduring clinical responses and experienced long-term survival advantages that persisted for a period of up to 10 years. The clinical endorsement of ipilimumab has paved the way for a kind of cancer immunotherapy known as ICT. Since then, the discipline of Information and Communication Technology (ICT) has made significant advancements by providing long-lasting therapeutic advantages, such as curing patients with different kinds of solid malignancies, and has resulted in many approvals from the FDA (17).

Programmed Death 1 (PD-1)

PD-1 is a T cell inhibitory checkpoint molecule that acts as a checkpoint in T cells. Its role as a checkpoint molecule was understood with the identification of its ligands, programmed death ligand 1 (PD-L1) and PD-L2. Experiments conducted using Pd1−/− mice demonstrated that the interaction between PD-1 and its ligands is responsible for preserving T-cell tolerance in the peripheral regions. PD-1 binding prevents TCR signaling by attracting the Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) and 2 (SHP-2) tyrosine phosphatases, which remove phosphate groups from molecules implicated in TCR signaling, such as CD3ε and ZAP-70 (18). PD-1 is abundantly present in T cells that have infiltrated tumors, particularly in T cells that are tired. Tumor cells and other kinds of cells inside the tumor, such as endothelial cells, epithelial cells, and myeloid cells, express PD-L1. On the other hand, PD-L2 is mostly expressed by antigen-presenting cells (APCs). Preclinical investigations have shown that the binding of PD-1 to PD-L1 in the tumor microenvironment (TME) hinders the ability of T cells to respond against tumors. On the other hand, blocking this relationship using anti-PD-1/PD-L1 antibodies enhanced the immune response of T cells against tumors, resulting in the shrinkage of tumors in several mouse tumor models (19). Anti-PD-1 and anti-PD-L1 antibodies have been shown effective in clinical trials for several kinds of tumors, including melanoma, tumors of the kidney (RCC), and non-small cell lung cancer (NSCLC). In 2014, the FDA granted first approval for the use of monoclonal anti-PD-1 antibodies to treat patients with metastatic melanoma. Subsequently, the FDA authorized additional immune checkpoint medications that target the PD-1/PD-L1 pathway for treating various kinds of tumors (20).

Pembrolizumab, a humanized IgG4 monoclonal antibody, was first authorized by the FDA for the treatment of metastatic melanoma and NSCLC. Over the following years, the treatment received approval for various types of tumors, such as squamous cell carcinoma of the head and neck (HNSCC), solid tumors with high microsatellite instability (MSI-H), progressed gastric cancer, cervical cancer, urothelial tumors, triple-negative breast cancer (TNBC), and tumors with the high mutational burden (TMB-H). The FDA has approved for pembrolizumab to be used in the treatment of advanced endometrial cancer that is MSI-H or mismatch repair-deficient (dMMR), based on the findings of the KEYNOTE-158 study (21).

Nivolumab, a completely human IgG4 monoclonal antibody, received FDA approval in 2014 for the treatment of melanoma. As a result, new uses were authorized for the treatment of NSCLC, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma, esophageal squamous cell carcinoma, pleural mesothelioma, and colorectal cancer (CRC) with deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) (22). In 2022, nivolumab received many successful approvals from

the FDA for several indications. The combination of Nivolumab and LAG-3 inhibitor has received approval for treating unresectable or metastatic melanoma, after the findings of the RELATIVITY-047 study. Furthermore, the combination of nivolumab and chemotherapy has been authorized as neoadjuvant treatment for early-stage NSCLC based on the findings of the CheckMate-816 trial (23). In addition, nivolumab has been granted permission for its use in conjunction with either chemotherapy or ipilimumab for patients diagnosed with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC), as indicated by the CheckMate-648 study (24).

PD-L1 Inhibitors

PD-1 can inhibit activated immune cells by interacting with its ligands, PD-L1 and PD-L2. PD-L1, often referred to as B7-H1, is extensively expressed in many kinds of tumors and immune cells, whereas PD-L2 is mostly found in normal dendritic cells. Tumors may manipulate the PD-1/PD-L1 pathway to weaken the immune response mediated by T-cells, resulting in the excessive growth of cancer cells. The comprehension of this interplay has become PD-L1 a compelling target for immunotherapy. Three PD-L1 inhibitors have been authorized by the FDA: atezolizumab, durvalumab, and avelumab (25, 26).

Atezolizumab, a humanized IgG1 anti-PD-L1 monoclonal antibody, received approval in 2016 for the treatment of urothelial cancer (27). As a result of the higher incidence of response, the diagnosis was subsequently extended to include NSCLC, SCLC, melanoma, and hepatic carcinoma. It is worth mentioning that the therapy was previously recommended for TNBC (triple-negative breast cancer), but it is no longer accessible as a therapeutic choice due to the failure to achieve the desired outcome in the IMpassion130 clinical study (28, 29). Durvalumab is a monoclonal antibody of the IgG1 class that specifically targets PD-L1 and was first authorized by the FDA for the therapeutic management of urothelial bladder cancer (30). After one year, the medication received approval for the treatment of stage III NSCLC and extensive stage SCLC (31). The FDA approved the use of durvalumab in conjunction with chemotherapy for patients diagnosed with biliary tract cancer (BTC) in 2022. This decision was made after the evaluation of the TOPAZ-1 clinical study (32). Avelumab, a completely human IgG1 anti-PD-L1 monoclonal antibody, received FDA approval in 2017. It was a significant advancement since it became the first therapy for metastatic Merkel cell carcinoma (MCC), a rare but aggressive kind of skin cancer (33). Subsequently, the therapy received approval for individuals diagnosed with urothelial carcinoma and renal cell carcinoma. Significant progress has been made in the development of novel CPIs for various indications (34).

Despite the rapid progress of CPIs as a kind of immunotherapy, their effectiveness might be hindered by many hurdles and limitations. Primary resistance, which refers to the tumor's lack of response to the first therapy, may occur in the context of CPI treatment. Furthermore, there might arise issues associated with acquired resistance, whereby the previously administered medicine becomes ineffective (35). Observations have been made in individuals with melanoma, indicating that around 30% initially exhibit a favorable response to treatment, but subsequently develop acquired resistance throughout the course of therapy. Another significant constraint in the use of CPIs is the emergence of immune-related adverse events (irAEs). This particular kind of undesirable incident may happen either at the beginning or later on in the course of the treatment regimen, and it presents itself in various ranges and levels. Moreover, other biological elements might directly or indirectly improve or restrict the CPI's performance, which will be further elaborated in the subsequent sections (35).

Additional immune regulatory molecules

Aside from CTLA-4 and PD-1, several additional immune regulatory molecules with positive and negative effects have been discovered and studied recently as possible targets for ICT. LAG-3 is abundantly present in activated T cells. It interacts with MHC class II, galectin-3, and α-synuclein. LAG-3 has immunosuppressive properties as it enhances the activity of Tregs and inhibits the function of T cells that carry out immune responses. LAG-3 specifically identifies stable MHC II: peptide complexes and triggers inhibitory signals via its intracellular domains upon attaching to them (36). Recent research has shown that the cytoplasmic tail of LAG-3 induces the separation of the tyrosine kinase, Lck, from CD4/CD8 co-receptors, resulting in a disruption of TCR signaling and the deactivation of T cells. Crucially, the injection of anti-LAG-3 antibody enhances the immune response of T cells against tumors in preclinical models (37). T cell immunoglobulin and mucin-domain containing-3 (TIM-3) is a molecule that acts as an inhibitory immunological checkpoint and is found in high levels on T cells that are malfunctioning or fatigued. TIM-3 interacts with galectin-9, high-mobility group protein B1, phosphatidyl serine, and carcinoembryonic antigen cell adhesion molecules by binding. 1 Significantly, the simultaneous targeting of the TIM-3 and PD-1 pathways has shown exceptional effectiveness in preclinical models of solid malignancies (38).

Unlike inhibitory checkpoint molecules, co-stimulatory molecules present in T cells enhance T cell-mediated anti-tumor immune responses. ICOS is a chemical that boosts the effectiveness of T lymphocytes by enhancing their effector activities. Furthermore, T cell effector activity is further enhanced by some members of the tumor necrosis factor (TNF) receptor family, such as glucocorticoid-induced TNFR-related gene (GITR), OX40, and 4-1BB, which serve as co-stimulators (39).

Primed T cells have a high level of expression of 4-1BB. Engaging 4-1BB with its ligand 4-1BBL increases the production of genes that prevent cell death in T cells, hence improving the long-lasting memory responses of cytotoxic T cells (39). Overexpression of 4-1BBL and the use of agonistic monoclonal antibodies that target 4-1BB enhanced the immune response of CD8 T cells against tumors and resulted in the rejection of tumors in preclinical models (39).

OX-40 is a co-stimulatory receptor that is expressed on T lymphocytes temporarily after they are activated (40). Activation of OX-40 by OX-40L improves the longevity of T cells and promotes the development of long-term memory. Furthermore, it hinders the activity of Tregs and the formation of induced Tregs. Significantly, increased levels of OX-40L and the use of agonistic anti-OX40 antibodies resulted in the greater rejection of tumors in several mouse models (40).

Diagnostic indicators of ICI-based immunotherapy

Several biomarkers, including PD-L1 expression, tumour mutation burden (TMB), microsatellite instability, microbiota, hypoxia, interferon-gamma (IFN-γ), and extracellular matrix, have been identified as potential factors that might enhance the reaction to immunotherapy for individuals receiving ICIs (41).

PD-L1 expression

PD-1 is a signaling receptor that is present on the outer surface of T cells. PD-1 and its ligand, programmed cell death PD-L1, have been extensively investigated in clinical trials as biomarkers for immunotherapy based on ICIs (4). The presence of PD-L1 was shown to be elevated by inflammatory agents, namely interferon-γ, in the TME. PD-L1 expression was also shown to hinder the protective function of CTLs and decrease the occurrence of persistent viral infections (42). Pathologists evaluate and quantify the PD-L1 expression using immunohistochemistry (IHC). One possible approach to enhance the immune system's ability to combat tumor cells is to target the PD-1/PD-L1 connection using monoclonal antibodies (mAbs) (43). This may lead to the suppression of this interaction. Research done by Bellmunt et al. assessed 542 individuals with advanced urothelial carcinoma and determined that Pembrolizumab had improved survival outcomes and fewer adverse effects compared to treatment (44). The KEYNOTE-522 trial conducted a comparison between patients who were administered Pembrolizumab plus chemotherapy and patients who were given placebo and chemotherapy. The study revealed that the former group had superior pathological results (45). The KEYNOTE-024 trial demonstrated that administering a fixed dosage of Pembrolizumab (200 mg) resulted in increased overall survival (OS) and progression-free survival (PFS), as well as reduced treatment-related side events, in NSCLC patients with a PD-L1 tumor percentage score (TPS) of 50% or higher, compared to chemotherapy (45). Moreover, the findings of the KEYNOTE-048 study indicated that Pembrolizumab enhanced overall survival (OS) in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) as the expression of PD-L1 increased (46). This highlights the significance of PD-L1 expression as an indicator of responsiveness to ICIs. The findings from CHECKMATE 040 have led to the approval of the combined medication of Nivolumab and Ipilimumab as a second-line treatment for HCC in patients who are already undergoing sorafenib (47).

Tumor mutation burden

Tumor mutational burden (TMB) refers to the number of mutations (muts) per megabase (Mb) in cancer cells. The threshold for TMB to be classified as high varies depending on the kind of tumor (thresholds of 10, 20, and >30 muts/Mb have been used in various studies). High tumor mutational burden (TMB-H) has been used as a promising biomarker to predict a substantial response to CPIs (48). A 2015 trial demonstrated a significant improvement in the objective response rate (ORR) and progression-free survival (PFS) among NSCLC patients with high tumor mutational burden (TMB-H) when treated with pembrolizumab. A separate trial demonstrated a strong correlation between the combination of nivolumab and ipilimumab and extended progression-free survival (PFS) in NSCLC patients with TMB-H. Furthermore, this positive response was sustained regardless of the absence of PD-L1 expression (49).

Furthermore, the KEYNOTE-158 research, which primarily focused on around 10 types of cancer (predominantly solid tumors), has shown a substantial treatment response in patients with TMB-H when treated with pembrolizumab. As a reaction, the FDA has approved for the use of the same medication in treating all solid tumors with a TMB-H of 10 or more mutations per megabase (50). Although both PD-L1 expression and TMB are used as biomarkers

to determine the effectiveness of CPIs, they do not exhibit a significant correlation in the majority of cancer types. Furthermore, they seem to function via separate processes to govern the response. While some data is suggesting that TMB may be a more reliable indicator of how well a patient would respond to CPIs compared to PD-L1 expression, the overall effectiveness of TMB in all types of solid tumors is uncertain and requires more research. For instance, individuals with glioma who have a low tumor mutational burden (TMB-L) but not a TMB-H have shown a positive response to CPIs. Although TMB has achieved a noteworthy achievement in predicting response to CPIs, there is still a need for a more dependable and all-encompassing biomarker(s) that has not been fulfilled (51).

Microbiota

The human body harbors microbiota in several regions, with notable concentrations in the skin, saliva, and gastrointestinal tract. The microbiome has the ability to impact ICIs treatment by modulating the immune system (52). A research conducted in live mice with CT26 tumors shown that a high level of microbial diversity may significantly enhance the response to ICIs by boosting the release of IL-2 and IFN- compared to animals treated with antibiotics (53). Consequently, there is a proposal suggesting that the microbiome can improve the immune response, trigger inflammation, or disturb the equilibrium between cell growth and cell death, ultimately leading to an increase in tumor formation (53). According to reports, the gut microbiota triggers T cell-mediated responses, leading to the specific attack on tumor cells. In addition, melanoma patients who received anti-PD-L1 treatment had elevated levels of *Bifdobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*, underscoring the significance of the microbiome (54). Zheng et al. recently published a study documenting dynamic changes in the gut microbiota of patients with HCC undergoing immunotherapy. Furthermore, the metagenomic sequencing data revealed a greater abundance of higher taxa in the fecal samples of patients who responded to immunotherapy, as opposed to those who did not react. This emphasizes the significance of the microbiome in controlling immune responses (55).

Extracellular matrix

The extracellular matrix (ECM) is a complex structure made up of large molecules outside of cells that offer biochemical assistance for tissues. Desmoplasia, also known as the proliferation of connective tissue, has been associated with a worse prognosis in patients with solid tumors (56). This is because there is a significant increase in collagen and fibroblast infiltration inside the TME. Stiffness is the main differentiating factor between normal and malignant ECM. Metalloproteases (MMPs) have the ability to degrade components of the ECM and produce smaller fragments of large molecules (57). These fragments may exhibit either pro- or anti-tumorigenic effects in certain forms of cancer. Consequently, fragments generated from collagen IV, such as tetrastatin, canstatin, and tumstatin, can decrease the invasiveness and proliferative characteristics of tumor cells by attaching to integrins (α3β1, α5β1, or αVβ3). In addition, Lysyl oxidase (LOX) hinders the movement of T cells to ECM and dampens the immunological response. The KPC model was employed to illustrate that the inhibition of LOX may enhance the infiltration of T cells, thereby leading to improved reaction rates to immunotherapy based on ICIs (58, 59).

New formulations of immune checkpoint inhibitors

Combining immune checkpoint drugs with chemotherapy

Clinical studies are now evaluating many combinations of ICT and chemotherapy regimens for the treatment of different types of malignancies. The phase III CheckMate 648 study, which included 970 patients with advanced, recurring, or metastatic esophageal squamous cell carcinoma, demonstrated that the combination of nivolumab with chemotherapy treatment resulted in a substantial improvement in OS as compared to chemotherapy alone (60). Moreover, clinical studies that have administered the combination of immunotherapy and chemotherapy to patients with NSCLC have shown a noteworthy increase in survival rates. The findings of the CheckMate 816 trial, which focused on patients with resectable NSCLC, demonstrated that the addition of neoadjuvant nivolumab alongside platinum-based chemotherapy resulted in enhanced event-free survival and a higher rate of pathological complete response. Specifically, 24% of patients in the combination group achieved a pathological complete response, compared to only 2.2% of patients who received chemotherapy alone (24).

These results provide a compelling justification to utilize this combination as the first therapy choice for individuals with advanced NSCLC. Furthermore, the use of carboplatin and etoposide in conjunction with anti-PD-L1 (atezolizumab) led to a notable enhancement in the median OS duration, increasing from 10.3 months (in the placebo group) to 12.3 months in the treatment group. This positive outcome prompted the FDA to approve the combination as the first treatment option for small cell lung cancer (SCLC) (61). It is important to mention that atezolizumab was granted rapid authorization by the FDA as an initial treatment for individuals with metastatic urothelial carcinoma, according to the findings of the IMvigor210 trial. However, recently

released findings from the phase III IMvigor130 trial (NCT02807636) demonstrated that the combination of atezolizumab and chemotherapy did not enhance overall survival when compared to chemotherapy alone. Further assessment is needed to evaluate the immunosuppressive influence of chemotherapy, taking into account factors such as dosage and timing. This evaluation should be conducted in appropriate preclinical studies that focus on particular tumor types, to enhance the effectiveness of combining chemotherapy with immunotherapy (62).

Immunological checkpoint inhibitors and radiation

Immuno-oncologic methods have the potential to improve radiation therapy in cancer treatment, and vice versa. Radiotherapy has a double impact on the tumor cells. It not only directly impacts the tumor cells but also modifies the immune environment in the TME (63). This is achieved by releasing tumor antigens, triggering a type I interferon (IFN) response, and enhancing the infiltration of effector CD8 T cells. Regrettably, the clinical studies including patients with metastatic NSCLC, metastatic head and neck squamous cell carcinoma, and Merkel cell carcinoma did not demonstrate any therapeutic effectiveness when radiation was combined with immune checkpoint inhibition. Nevertheless, significant pathological reactions showed up among individuals with early-stage NSCLC when stereotactic body radiotherapy was combined with neoadjuvant durvalumab. This indicates that the effectiveness of radiation when combined with immune checkpoint inhibition may vary depending on the stage of the illness and the timing of therapy (64, 65).

Immune checkpoint inhibitors with oncolytic viruses

Utilizing various methods, such as oncolytic viruses (OVs), to enhance the immune response has become increasingly popular. OVs offer a distinct advantage by specifically targeting cancer cells, replicating within them, and causing their destruction. This process also leads to the release of tumor-specific antigens, which trigger IFN signaling and create an inflammatory TME (66). Currently, there is just one medication called talimogene laherparepvec (T-VEC) that has been licensed by the FDA to treat the symptoms of individuals with advanced melanoma. T-VEC is a therapy that utilizes the herpes simplex virus 1 (HSV-1). The Phase 1b research, which combined T-VEC with anti-CTLA4 in incurable melanoma, demonstrated a substantial improvement in overall response rate (ORR) compared to ipilimumab alone. The ORR was 39% with the combination therapy, whereas it was only 18% with ipilimumab alone. The responses were observed in both the injected skin and visceral lesions (67).

Nevertheless, the recent phase 3 MASTERKEY-265 research, which had a larger sample size, compared the efficacy of T-VEC with pembrolizumab as a single agent. The study revealed an enhanced overall response rate (48.6% vs. 41.3%). However, it failed to achieve its main objectives of progression-free survival (PFS) and OS. Thorough correlation analyses of the tissues are necessary to evaluate how OVs affect immune modulation, the impact of long-term interferon stimulation, the selection of ICT, and the design of the clinical trial. These factors are crucial in comprehending the underlying causes for the absence of survival advantages, despite observed responses with this logical combination (68).

Combining immune checkpoint inhibitors with operation

The administration of systemic treatments to attain pathological reactions and enable the operation is well-recognized in several kinds of tumors, such as the application of neoadjuvant chemotherapy for the management of breast cancer or urothelial carcinoma. Moreover, the neoadjuvant condition enables the analysis of the whole tumor specimen, which offers enough tissue for comprehensive immune surveillance to determine the fundamental causes of both treatment response and resistance. During our presurgical clinical study of ipilimumab in individuals with bladder cancer, we observed the presence of ICOShiCD4 T cells in tumor tissues and later in the bloodstream. This finding establishes ICOShiCD4 T cells as a pharmacodynamic marker for anti-CTLA-4 treatment (69). Further investigations have verified the practical significance of the ICOS/ICOSL pathway in reaction to anti-CTLA-4 treatment, which supports the idea of combining therapies (69).

Neoadjuvant ICT has shown encouraging efficacy in several kinds of tumors, such as high-risk, human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, non-small cell lung cancer, and muscle-invasive bladder cancer. Research indicates that the timing of information and communication technology (ICT) about surgery has an impact on the body's reactions. In mouse models of spontaneously breast cancer metastasis, neoadjuvant anti-PD-1 treatment significantly decreased the spread of cancer to other parts of the body (70). This effect was not seen with adjuvant immunotherapy, which suggests that the prolonged reaction of tumor-specific CD8 T cells may be responsible for the reduction in metastases. This response may be linked to the discharge of tumor antigens caused by surgery. However, ICT has shown advantages in the adjuvant treatment of some kinds of tumors, including melanoma and NSCLC. However, there is inconsistent evidence about its effectiveness in other tumor types, like renal cancer (71).

Immune-related toxic reactions to ICIs

The immunological response to ICIs exhibits

variability, distinct from the response seen with conventional chemotherapy. A multitude of folks encounter adverse consequences, including weariness, dermatological eruptions, and colitis (inflammation of the colon). Certain individuals may encounter a strong response, known as an immune-related adverse event (irAE) (72). irAEs may have a profound influence on several organs, including the gastrointestinal system, skin, liver, endocrine glands, myocarditis, and others. The incidence of adverse events resulting from irAEs caused by ICIs varies depending on the particular medication and the individual patient's health profile. The predicted fatality rate associated with these medicines ranges from 0.3% to 1.3%. Severe or negative side effects from immunotherapy medications often manifest early in the course of treatment and may be significant (73). Nevertheless, the risk associated with this treatment is relatively reduced in comparison to other medical interventions like as chemotherapy or stem cell transplantation. The kind of adverse effects may also differ depending on the specific mix of medications used. Colon inflammation-related mortality is more prevalent among patients undergoing treatment with anti-CTLA-4 medications, while mortality due to lung inflammation is more common in individuals getting anti-PD-1 or anti-PD-L1 therapies (73).

Adverse events (irAEs) resulting from the delivery of anti-CTLA-4 antibodies occur in sixty percent of patients who receive treatment and might vary in severity. Out of them, a significant proportion of ten to thirty percent of individuals encounter severe (grade 3-4) irAEs. The incidence of irAEs is directly proportional to the dosage, meaning that larger dosages are more likely to result in a greater occurrence of negative side effects. The majority of grade ≥ 3 irAEs occur within 8-12 weeks after starting the medication. The occurrence of skin rash occurs earliest, whereas diarrhea and/or colitis are the most common irAEs resulting from the delivery of anti-CTLA-4 antibodies. Additional toxicities include endocrinopathies, hepatotoxicity, and infrequent toxicities like neuropathies, autoimmune thrombocytopenia, and syndromes resembling Stevens-Johnson syndrome. Neurological irAEs manifest in 3.8% of patients receiving anti-CTLA-4 antibodies, with serious side effects of grade ≥ 3 occurring in fewer than 1% of individuals (74).

Anti-PD-1 antibodies had a lower occurrence of irAEs compared to anti-CTLA-4 antibodies. The majority of Anti-PD-1-related irAEs occur during the first 6 months after initiating medication treatment. Typical side effects (seen by fewer than 25% of patients) include skin rash, tiredness, joint pain, headache, itching, diarrhea, inflammation of the colon, inflammation of the lungs, liver inflammation, and hormonal disorders. The incidence of grade ≥ 3 irAEs is around 10% in patients treated with anti-PD-1 medicines, however, it may reach up to 30% in patients treated with anti-CTLA-4 antibodies. Neurological irAEs manifest in around 2.9% of patients who undergo anti-PD1 medication (75). Nevertheless, the occurrence of cutaneous, hepatic, and pulmonary-related irAEs is more common when administering anti-PD1 antibodies compared to anti-CTLA4 antibodies. Conversely, thyroid and lower digestive tract irAEs, such as colitis, are more prevalent with anti-CTLA4 antibody administration. There is a suggestion that tailored immunosuppression, using anti-PD-1 antibodies together with antibodies that target specific inflammatory mediators, might prevent the worsening of autoimmune illnesses. This can be done without affecting the effectiveness of anti-PD-1 medications. In the event of irAEs, one might consider attempting the management, monitoring, and withdrawal of the medicines (75).

Outlook and conclusion

ICIs, or immune checkpoint inhibitors, function in collaboration with the immune system and represent a significant advancement in the field of cancer therapy. They assist in bolstering and intensifying the body's innate immunological response to cancer, resulting in an enhanced anti-tumor reaction. These medications have completely transformed the approach to cancer treatment, and they possess the capacity to further influence patient outcomes substantially in the future. Nevertheless, similar to other cancer therapies, ICIs may result in adverse effects, including immune-related adverse events (irAEs) such colitis, hepatitis, and dermatological responses. These adverse effects may often be controlled with timely identification and intervention. The potential of ICIs in cancer therapy is very promising for the future (76).

Nevertheless, despite the notable efficacy of ICIs in cancer treatment, there are instances when their effectiveness may be limited or malignancies may develop resistance to ICIs, necessitating the use of alternate therapeutic strategies. This encompasses tumors characterized by a low TMB, low expression of PD-L1, an immunosuppressive tumor microenvironment, or alternate mechanisms of immune evasion. Cancers characterized by a low TMB, such as particular forms of breast and prostate cancers, may lack a sufficient number of neoantigens (antigens resulting from tumor-specific mutations) to elicit a strong immune response. Similarly, tumors with low expression of PD-L1 are not effectively responsive to PD-1/PD-L1 inhibitors. The presence of regulatory T cells, myeloid-derived suppressor cells, and other immune-suppressive components in tumors with an immunosuppressive microenvironment hampers the efficacy of ICIs (77).

Targeted, combined, adoptive, or vaccine-based

therapy may be beneficial in such instances. The combination of ICIs with other treatments, including chemotherapy, radiation, specific treatments, or other immunotherapies, might potentially improve the overall therapeutic response. It can additionally involve focusing on a pair or group of ICIs. The concurrent use of ICIs with numerous therapeutic agents is a very active area of research and clinical advancement in the area of cancer immunotherapy. The objective is to combine several methods of action, amplify the total immune response against tumors to combat resistance and increase the results for patients. This has been well evaluated elsewhere (78).

This study primarily examined CTLA-4, PD-1, and PD-L1, but it also identified other potential targets for ICIs that show promise. Some examples of these are LAG-3, TTIM-3, TTIGIT, VVISTA, and B7-H3 inducible T cell costimulatory (ICOS) (79). Clinical studies are being conducted to test inhibitors that target these receptors. However, the effectiveness of these inhibitors may change depending on the specific kind of cancer and the characteristics of the patients. Therefore, it is crucial to conduct thorough clinical trials to evaluate the safety and effectiveness of these inhibitors (78).

In the future, research on ICIs is anticipated to progress further, resulting in the creation of immunotherapies that are both more efficient and safer. Future research is expected to concentrate on novel inhibitor development, combination treatment, and exploration of unexplored malignancies. In addition, the efficacy of ICIs might differ across patients, and scientists are investigating methods to distinguish individuals who react positively to ICIs from those who do not. This might potentially result in the advancement of individualized medical strategies, whereby patients are administered the most probable medication to yield positive outcomes for them. Furthermore, the identification of biomarkers that may accurately predict the response to these medicines has the potential to inform treatment choices and ultimately improve patient outcomes.

Authors' Contribution

Akram Sadat Ahmadi and Atefeh Valaei were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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The authors declare no conflict of interest.

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A Case Report of Combination Maintenance Therapy with Olaparib and Bevacizumab in Advanced Ovarian Cancer: A Promising Approach

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Abstract

Epithelial Ovarian Cancer (EOC) is a common and often deadly disease among women, with High-Grade Serous Ovarian Carcinoma (HGSOC) making up about 75% of cases. Standard treatment includes surgery and platinum-based chemotherapy. Recent studies highlight the effectiveness of Poly (ADP-Ribose) Polymerase (PARP) inhibitors, especially for patients with BRCA1/2 mutations or Homologous Recombination Deficiency (HRD). HRD status is a key biomarker for predicting PARP inhibitor success, even without BRCA mutations. Genomic signatures can detect HRD independently. Healthcare professionals assess HRD by evaluating genomic instability and recommend PARP inhibitors for patients with an HRD score of 42 or higher. Combination maintenance therapy with Olaparib and Bevacizumab has shown improved survival for HRD-positive or BRCA-mutated patients. A case report of a 36-year-old woman with advanced ovarian cancer showed a positive treatment response and tumor-free lymph nodes after neoadjuvant chemotherapy, surgery, and targeted therapy. Combination maintenance therapy with a PARP inhibitor and Bevacizumab is crucial in advanced ovarian cancer treatment.

In conclusion, a combination of a PARP inhibitor and bevacizumab for maintenance therapy is essential in the treatment of advanced ovarian cancer. Patients in stages 3 and 4 gain significant benefits from this approach, which is customized according to their initial treatment, BRCA mutation status, and Homologous Recombination Deficiency HRD status.

Keywords: Epithelial Ovarian Cancer, High Grade Ovarian Carcinoma, Homologous Recombination Deficiency, Olaparib Bevacizumab

Introduction

Epithelial ovarian cancer (EOC) is a widespread and often deadly illness that affects women all over the world. Approximately 75% of all EOC cases are due to high-grade serous ovarian carcinoma (HGSOC). Unfortunately, most patients are not diagnosed until the disease has progressed to an advanced stage (III-IV). The typical treatment for newly diagnosed EOC

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usually involves surgery to remove as much of the tumor as possible, followed by chemotherapy using platinum-based drugs. However, recent clinical trials have shown that maintenance therapy with Poly (ADP-ribose) polymerase (PARP) inhibitors can be beneficial, especially for patients with BRCA1/2 mutations or homologous recombination deficiency (HRD). HRD status is an important biomarker that can help identify patients without BRCA mutations who could still benefit from PARP inhibitors as a first-line maintenance treatment.

Epithelial ovarian cancer EOC is a prevalent and often fatal disease affecting women worldwide. high-grade serous ovarian carcinoma HGSOC accounts for approximately 75% of all EOC cases. Unfortunately, most patients are diagnosed at an advanced stage (III-IV) (1-7). The standard treatment for newly diagnosed EOC typically involves cytoreductive surgery followed by systemic platinum-based chemotherapy [8,9]. However, recent clinical trials have underscored the benefits of maintenance therapy with Poly (ADP-ribose) polymerase PARP inhibitors, especially for patients with BRCA1/2 mutations or homologous recombination deficiency HRD As a critical predictive biomarker, HRD status helps identify BRCA wild-type patients who may benefit from PARP inhibitors in the first-line maintenance setting (10-14) .

Approximately 50% of EOC cases exhibit HRD due to alterations in homologous recombination repair (HRR) pathway genes, making HRD a significant predictive biomarker for ovarian cancer treatment (15, 16). Genomic scar signatures can indicate the presence of HRD even in the absence of BRCA mutations, though the incidence of BRCA1/2 mutations in EOC is only around 30% (17-19).

Healthcare professionals calculate an HRD score by assessing three measures of genomic instability: Loss of heterozygosity (gLOH), which is the permanent loss of one allele copy of a gene; the number of telomeric allelic imbalances (TAI), referring to regions with allelic imbalances; and large-scale transitions (LST), which involve genomic alterations associated with chromosome breakages. An HRD score of 42 or greater is considered positive, indicating that a patient may be a candidate for targeted treatment with PARP inhibitors, regardless of BRCA1/2 mutation status (20).

Given that ovarian cancer patient who are HRD-positive or have BRCA mutations benefit from combination maintenance therapy with olaparib and bevacizumab, which has been shown to improve overall survival and progression-free survival, we utilized this combination maintenance therapy for the patient, in this case, report (21).

Case presentation

A 36-year-old woman presented with abdominal pain that had persisted for 9 months. After an initial ultrasound examination, a CT scan was recommended. The CT scan revealed a heterogeneous lesion measuring 62 x 40 millimeters, with adhesions and pressure on the intestinal loop. The primary probable origin was thought to be tubo-ovarian. Additionally, the left ovary appeared enlarged and contained multiple cysts.

Further evaluation included tumor markers, which showed elevated CA-125 levels (96). A PET-CT scan was performed, revealing an irregularly bordered cystic lesion in the left adnexa and hypermetabolic subcapsular lesions in hepatic segment VII. Extensive peritoneal metastasis involving the small bowel wall was also observed, suggesting a possible origin from the adnexa or colon (Figure1).

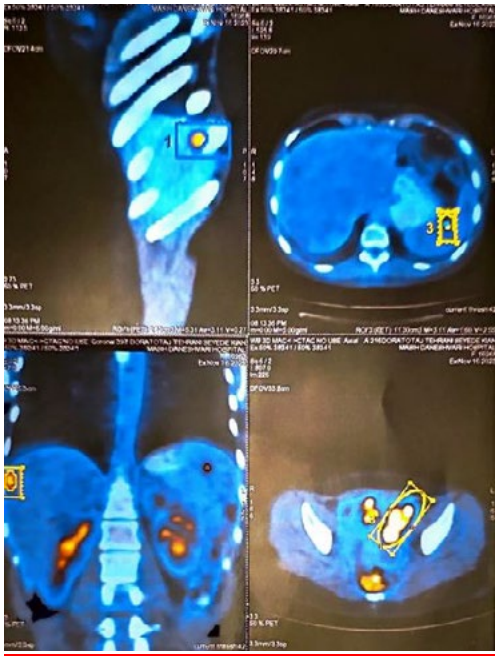

Fig 1. The patients' PET scan results.

Following a diagnostic laparoscopy, the patient had signs of ascites and peritoneal involvement. Biopsies from the omentum and peritoneum, as well as the cytology of the ascitic fluid, were unable to identify the exact kind of tumor. After immunohistochemistry, positive markers that are indicative of high-grade Müllerian serous carcinoma were found. The diagnosis was validated by molecular analysis by next-generation sequencing. The patient started neoadjuvant treatment with carboplatin and paclitaxel after being staged as per FIGO stage IIIc. When the therapy response was evaluated by MRI after three cycles, a partial response was seen. After six rounds of neoadjuvant chemotherapy, the patient underwent bilateral hysterectomy and oophorectomy. The subsequent cycles proceeded. High-grade serous carcinoma encompassing the ovaries, liver, and

omentum was found in the postoperative pathology. The cervical, iliac, and obturator areas as well as the aortocaval lymph nodes. Considering the final NGS results, the patient was a candidate for PARP inhibitor therapy (due to the unavailability of type 3 inhibitors) in combination with bevacizumab.Lymph nodes in the iliac, obturator, and aortocaval regions, as well as cervical tissue, were tumor-free. Based on the final NGS results.

Three months into treatment, a PET-CT scan confirmed a complete metabolic response. Therefore, the combined therapy was continued (Figure2).

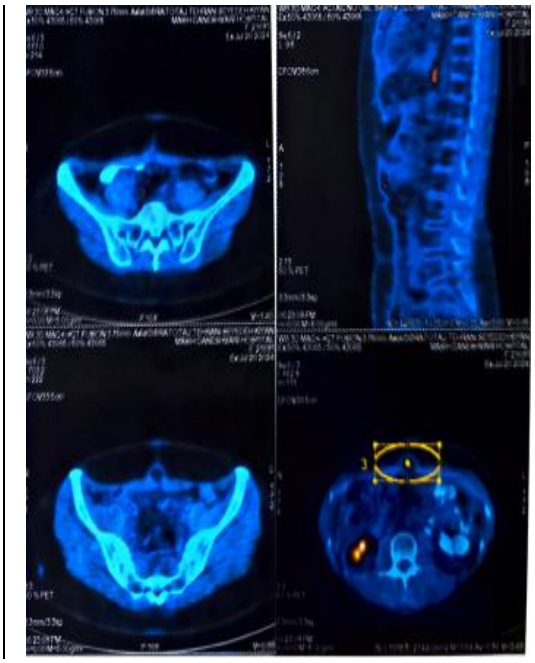

Fig 2. The patients' PET scan results.

Discussion

In this case, the significant role of combination maintenance therapy with a PARP inhibitor and bevacizumab in advanced ovarian cancer has been highlighted. Maintenance therapy is standard for patients with ovarian cancer in stages III to IV, and the specific type is determined based on the patient's initial treatment, BRCA mutation status, and homologous recombination deficiency HRD status (22).

Generally, patients with stage 3 and 4 ovarian cancers may have more benefit from neoadjuvant therapy compared to primary surgery. The initial neoadjuvant therapy for these patients includes a platinum-based chemotherapy regimen. Adding bevacizumab to the neoadjuvant treatment regimen has been investigated in various studies and may be added based on the patient's condition, tumor characteristics, and the physician's discretion (23). In the GOG-0218 and ICON7 trials, patients who received carboplatin and paclitaxel in combination with bevacizumab, followed by maintenance therapy with bevacizumab alone, showed an increase in median progression-free survival (PFS) (24, 25).

In general, for ovarian cancer patients, it is particularly important to plan maintenance therapy for those at higher risk. This includes patients with stage IV disease, inoperable stage III, suboptimally debulked stage III (with residual disease greater than 1 cm), poor performance status, high-grade serous histology, and elevated pretreatment CA-125 levels (26-28).

Both the GOG-0218 and ICON7 trials found that patients receiving bevacizumab during chemotherapy had a slight decline in quality of life (QOL). However, this decline did not continue into the maintenance phase (24, 25).

Randomized trials have recently investigated the use of PARP inhibitors as maintenance therapy after first-line chemotherapy for patients with newly diagnosed and histologically proven FIGO stage III/IV ovarian, fallopian tube, or primary peritoneal cancer (29) .

In the SOLO-1 trial, olaparib as a single agent significantly improved progression-free survival (PFS) compared to placebo when used as maintenance therapy. This benefit was seen in patients with either germline or somatic BRCA1/2 mutations who had achieved a complete or partial response after first-line platinum-based chemotherapy. A later subgroup analysis confirmed that the PFS benefit was significant for both BRCA1 and BRCA2 mutation types (30) .

In the PAOLA-1 trial, progression-free survival (PFS) was dramatically increased by combining olaparib with maintenance bevacizumab. Patients with advanced ovarian cancer who responded completely or partially to bevacizumab and platinum-taxane treatment in the first line saw this advantage. PAOLA-1 comprised individuals with and without BRCA1/2 mutations, in contrast to SOLO-1. Subsequent sub-analysis revealed that whether the BRCA mutation was BRCA1 or BRCA2, the PFS benefit of adding olaparib to bevacizumab maintenance was the same (21) .

Patients without BRCA1/2 mutations were further categorized based on Genomic Scar Analysis (GSA) results. PFS was significantly improved for those with homologous recombination deficiency (HRD) but not for those without it. with the availability of next-generation sequencing (NGS) technology, tumor molecular analysis should be recommended for all patients (18-21).

In the mentioned patient, considering the early stage, neoadjuvant therapy was initiated. Due to concerns about the adverse effects of bevacizumab (such as bleeding and gastrointestinal perforation), a combination of dual chemotherapy (carboplatin and paclitaxel) was chosen (31) .

Based on the post-surgery pathology results, which indicated residual disease, high risk criteria,

and positive genomic markers (BRCA wild-type and positive HRD), the decision was made to proceed with maintenance therapy using the combination of bevacizumab and olaparib. Three months after starting the treatment, a follow-up PET scan showed that the patient was in complete metabolic response. Therefore, the continuation of treatment with the same combination was planned (32).

Conclusion

In advanced ovarian cancer, combination maintenance therapy with a PARP inhibitor and bevacizumab plays a crucial role. Patients in stages 3 to 4 benefit from maintenance therapy, tailored based on initial treatment and BRCA mutation and HRD status. Neoadjuvant therapy may offer more advantages than primary surgery for stage 3 and 4 ovarian cancer patients. Adding bevacizumab to neoadjuvant treatment has shown promise, but individualized decisions are essential. Genomic scar analysis (GSA) further informs treatment decisions. Overall, tumor molecular analysis using next-generation sequencing NGS should be recommended for all patients (33).

Statements and Declarations

Consent to participate and Publication

The patient provided informed consent for participation in this case report and publication. She understood the purpose, risks, and benefits of sharing her medical information for scientific and educational purposes. Confidentiality was maintained, and her initials were used to protect privacy. We seek to share this unique case to contribute to medical knowledge and improve patient care.

Availability of data and materials

The availability of data and materials is subject to institutional policies, patient consent, and legal constraints. Researchers should follow established protocols and guidelines when requesting access to clinical information.

Ethics approval and consent to participate

Ethical considerations guided decision-making, ensuring patient autonomy, safety, and adherence to best practices.

Conflicts of Interest

The authors affirm that they have no conflict of interest.

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Authors' contributions: Soodeh Ramezaninejad: investigation and writing. Maedeh Mataji: investigation and writing.

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Present Developments in the Creation of Sophisticated Acinetobacter Therapies

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Abstract

Acinetobacter baumannii is a common global source of infections linked to healthcare that have a high morbidity and fatality rate. Due to the fast emergence of multidrug-resistant and very drug-resistant strains of A. baumannii, the therapeutic management of these infections has become much more challenging. Therefore, the creation of innovative intervention techniques is desperately needed to counteract this infection, which is resistant to several drugs. One of the best medical treatments for infection management is vaccination, which also has the potential to prevent A. baumannii from developing multidrug resistance. Here, we focused on the three most crucial preclinical vaccine development steps: immunological correlates of protection, antigen selection, and model organisms for effectiveness assessment. We also highlighted current developments and future obstacles in the production of A. baumannii vaccines.

Keywords: Genomic analysis, Autoimmune disorders, Personalized medicine.

Introduction

Acinetobacter baumannii is a commonplace extracellular gram-negative bacterium that is linked to a significant number of healthcare-associated illnesses (HAIs) both in hospitals and the community (1). Additionally, infections resulting from natural disasters or battle wounds are often caused by *A. baumannii* (1, 2). The infection is often linked to a high morbidity and death rate and may cause a wide range of illnesses, including meningitis, pneumonia, and major bloodstream or soft tissue infections. The fast emergence of multidrug-resistant and highly drug-resistant strains of *A. baumannii* has made the medical management of these infections more challenging. Furthermore, *A. baumannii* frequently creates biofilms that are impervious to both host defensive mechanisms and antibiotic therapy. Therefore, the creation of innovative intervention techniques is desperately needed to fight and manage multidrug-resistant *A. baumannii* infections (3).

Epidemiology

New pathogens are emerging, which is causing changes in nosocomial infection frequencies. Abuse of antibiotics is also causing changes in antibiograms (4). *A. baumannii* was singled out for alerts according to surveillance data because of its high tenacity on inanimate items in intensive care units (ICUs) for extended periods (5). Furthermore, *A. baumannii* developed resistance to practically all-powerful antibiotics quickly, lengthening the duration of an ICU stay. Seasonal conditions,

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patient instances, and catastrophe dates were all connected with outbreaks. According to research, *A. baumannii* is more common in late summer to early winter, peaking at 50% from July to October and preferring wet and damp environments (5). Reports of *A. baumannii* were common during wartime, for example, in Afghanistan and Iraq. It was discovered that, as opposed to the trauma itself, morphine used as an analgesic in combat zones amplifies the spread of *A. baumannii* infections (5). *A. baumannii* did not only thrive during wartime but also natural calamities like the aftermath of the 1999 Marmara earthquake (5, 6) and the 2004 Asian tsunami (5, 6).

Therapy

Many antibiotics, including trimethoprim, amoxicillin (penicillins), narrow-spectrum cephalosporins, Ertapenem, and chloramphenicol, are naturally resistant to *A. baumannii* (7). *A. baumannii* was able to transfer plasmids, transposons, and integrons from other Gram-negative bacteria, which allowed it to acquire resistance genes against many types of antibiotics. The capacity to eject aminoglycosides, rifampicin, quinolones, fluoroquinolones, tetracyclines, and some disinfectants were all factors in *A. baumannii* resistance. As a result, many multi-drug resistance (MDR) *A. baumannii* strains have emerged and caused notable epidemics in numerous nations worldwide, with notable regional variations. The use of bacteriophages, prophages, levamisole, an anti-helminthic that is effective against *Acinetobacter lwoffii*, the use of nanoparticles producing nitric oxide, photodynamic therapy, and radio-immunotherapy were among the atypical therapeutic options brought about by the lack of an effective treatment for *A. baumannii*. Nevertheless, there are still safety issues with its use (8, 9).

Immunostimulants

One of the best medical treatments for infection management is vaccination, which also has the potential to prevent the pathogen from developing medication resistance (10). There are currently few viable antibiotics on the market or in the late stages of research that can be used to treat infections caused by *A. baumannii* that are resistant to several drugs. Therefore, the burden of *A. baumannii* infections would be significantly reduced by the development of safe and efficient *A. baumannii* vaccines for both active and passive vaccination. After being started by Pachon and McConnell, *A. baumannii* vaccine development for specific populations has started in several labs worldwide, and various experimental vaccination trials have been published (11). Several outstanding studies have lately assessed the requirements and financial benefits of an *Acinetobacter* vaccine, as well as the advancements in science and probable difficulties in *A. baumannii* vaccine development's clinical trials. Although advancements and efforts have been made, the development of *A. baumannii* vaccines has lagged behind that of other nosocomial pathogens (like Clostridium difficile, Staphylococcus aureus, etc.). Additionally, no *Acinetobacter* vaccine has entered a Phase I clinical trial to date, indicating the relative difficulties in creating safe and effective *A. baumannii* vaccines. Here, we focused on the three most crucial preclinical vaccine development processes while discussing current developments and future obstacles in the development of *A. baumannii* vaccines: correlations between antigen selection correlates of protection and animal models for efficacy evaluation (12).

Selection of vaccine antigens

The immunogen in the early investigations on the *A. baumannii* vaccine was inactivated whole cells or components of cells (OMVs and OMCs) (13). The findings of such investigations have amply supported the viability of developing vaccines against *A. baumannii*. Animals (mostly mice) immunized with those vaccines develop antigen-specific antibody responses, which protect against a challenge involving different clinical and ATCC typing strains of *A. baumannii*. The challenge results in significantly lower bacterial burdens in tissue and blood, as well as a reduction in the inflammatory responses that accompany it (14). Despite the vaccines' excellent efficacy, possible safety and regulatory issues restrict their clinical usage. Therefore, determining which antigens best elicit the protective immune response has a major positive impact on vaccination safety and production. However, the expected heterogeneity in O-antigen and CPS demonstrated by various *A. baumannii* strains and samples is likely to challenge the glycoconjugate method (15). Even though almost all *A. baumannii* serovars were found in the early research, more is needed to know how common these serovars are among clinical isolates. According to recent research, 13% of the 100 *A. baumannii* strains examined were recognized by a monoclonal antibody targeting *A. baumannii* K1 CPS, demonstrating the relative variety of this pathogen's surface carbohydrate antigens (16). To ascertain which serotypes are more likely to be connected with a certain illness or are very common, further epidemiological research would be required to identify the optimal vaccine candidate. In this context, various bacterial pathogens, including *A. baumannii*, generate poly-N-acetyl-b-(1-6)-glucosamine (PNAG), a surface exopolysaccharide. Researchers demonstrated that antiserum to 9Glc-NH(2)-TT was strongly opsonic against different unrelated clinical strains of *A. baumannii* that synthesize varying quantities of surface PNAG by

conjugating a synthetic that resembles PNAG to tetanus toxoid (TT) (17). More crucially, compared to mice given a placebo, treatment with those antisera dramatically decreased the amounts of bacteria in the blood and lungs, indicating that PNAG could be a viable antigen for eliciting protective antibodies that cover a wide range of serotypes. The use of protein antigens or multivalent glycoconjugate vaccines against extremely common *A. baumannii* serotypes, as in the situation of S. pneumoniae, are two additional methods to offer a comprehensive coverage of the various serotypes (18).

Immunological correlates of defense versus infections caused by *A. baumannii*

The development of *A. baumannii* vaccines has advanced significantly over the past five years. However, before a vaccine candidate can go into clinical trials, more work may need to be done to improve the vaccine's protective effectiveness in terms of survival rates and tissue and blood-bacterial burdens. This will thus need a deeper comprehension of protective immunity's processes and possible correlates of protection (19).

Experiments demonstrate the much-anticipated function that certain antibodies play in the vaccine-induced defense against *A. baumannii* infection. The following findings have been reported: (1) the protection against *A. baumannii* challenges was recapitulated by passive transfer of entirety sera from vaccinated or convalescent animals toward polyclonal or monoclonal antibodies toward the whole *A. baumannii* cells or its cell elements; (2) anti-OmpA antibody levels are associated with survival in mice; (3) opsonization of K1-positive *A. baumannii* strains, but not K1-negative varieties, with a specific monoclonal antibody significantly enhanced neutrophil-mediated bactericidal action in vitro; and (4) vaccinations of B cell-deficient mice were unable to elicit a protective immunity toward subsequent *A. baumannii* challenges. Conversely, the mechanism behind antibody-mediated defense against *A. baumannii* needs to be better understood (20). Research has shown that immunological sera promote *A. baumannii* opsonophagocytic death but not complement-mediated death. Conversely, some research has shown that the opposite is true. It was also rather surprising to learn that FcRg-/- mice maintained the immunity established by the immunization (21).

Animal models for developing a vaccination against *A. baumannii*

The employing of animal models with clinical significance is essential to the effective creation of vaccines, as it is in the majority of vaccine studies and development (22). The mouse continues to be the most often utilized laboratory animal species for assessing the effectiveness of the *A. baumannii* vaccine. The first mouse models were created using either virulence-enhancing (like porcine mucin) or immunosuppressive (like cyclophosphamide) drugs to guarantee or promote the growth of a persistent infection. Replicable *A. baumannii* infections in immune-competent and traditional mouse strains have been successfully created by several organizations recently (23). *A. baumannii* pneumonia and wound infection in rats also resemble many features of clinical illness in humans. Immunocompromised animals mimic the conditions of human *A. baumannii* infections, which typically occur in immunocompromised individuals; conversely, the employing of immune-competent animals would allow the identification of the critical immune components that are essential to the host's response toward *A. baumannii* infection. Using multiple animal models could facilitate the development of secure and efficient *A. baumannii* vaccines (24).

The *A. baumannii* vaccine study group must rationally choose suitable animal models for vaccine efficacy evaluation in addition to standardizing vaccine immunity and effectiveness evaluation procedures (such as the time intervals between vaccinations and challenge, as well as the challenge varieties, doses, and routes, among other things) to compare the experimental vaccines' efficacies across laboratories (25). Regarding this, it was observed that the quantity of OmpA utilized in vaccines has a significant influence on the immunodominant epitope protection and immune responses elicited; a high dose promotes a Th2-biased response, while a low dose induces a balanced Th1/Th2 response. This may account for the variations in the vaccine's protective efficacies reported by various (26). The evaluation of protection against challenges posed by different clinical isolates in addition to challenges by homologous strains in several *A. baumannii* vaccination trials are positive as they help determine the vaccine candidate's overall level of protection. Nonetheless, the majority of the research could have described the challenge strains' serotypes or genetic diversities. Apart from the previously reported strain-specific changes in surface carbohydrate antigens, there is also significant heterogeneity in the proteomic patterns and biological functions of OMVs derived from several *A. baumannii* strains (27, 28).

Conclusion

As an aggressive, resistant superbug, *A. baumannii* has become more widespread, creating outbreaks that have led to high rates of morbidity and mortality, particularly in people who are already vulnerable. Because *A. baumannii* is difficult to identify, it

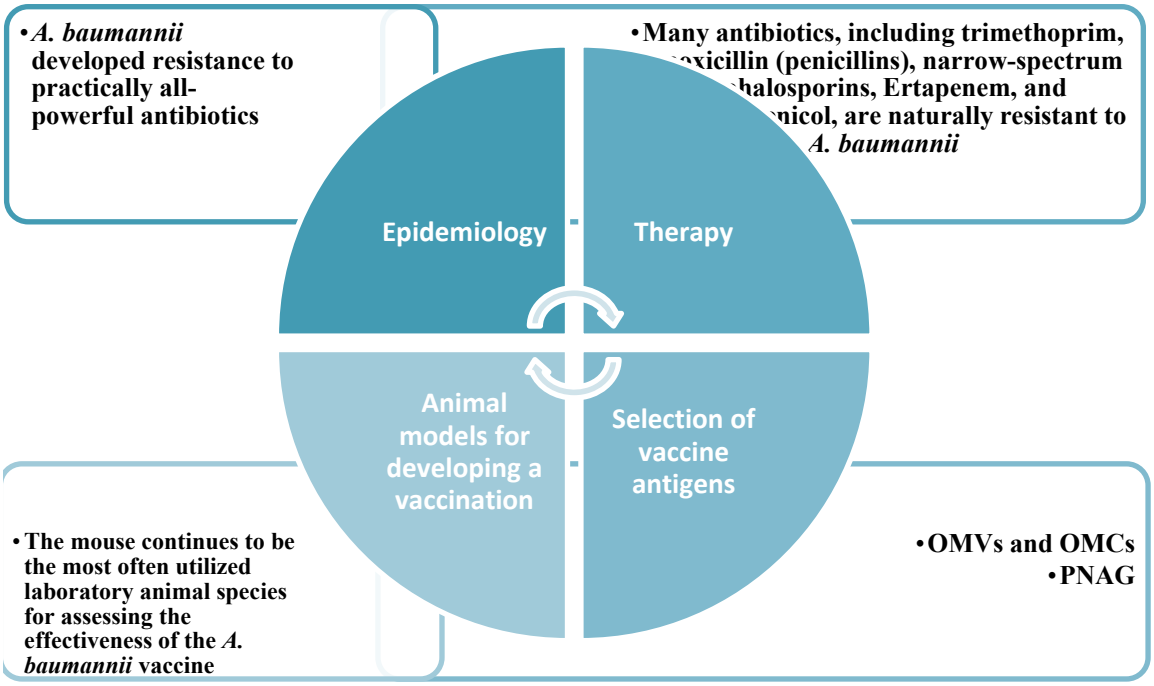

Fig1. Acinetobacter baumannii treatment flowchart.

takes time and expensive equipment, especially when trying to save lives. The rapid development of antibiotic resistance in *A. baumannii* makes it difficult to control and has already ended the antibiotic golden age. The supply of new antibiotics to combat the *A. baumannii* invasion has run out, and all other treatments are still in the research and development stage and will take years to reach the market. Therefore, ending the vicious cycle from its inception makes perfect sense in addition to infection management. Although the Australian group's groundbreaking work using in silico techniques to screen *A. baumannii*'s antigenic determinants was a good first step toward identifying effective epitopes, it was not entirely successful because *A. baumannii* contains some immune-dominant antigens that may obscure other effective antigens in the pathogen.

Furthermore, polysaccharide epitopes are never predicted by in-silico-based techniques; only protein epitopes are. Consequently, the mere use of those suggested epitopes would not be very beneficial, and more research using binding methods is required to provide a powerful vaccination against *A. baumannii*. In light of the trial-and-error nature of miss-guided empirical vaccine manufacture, it is evident now how important epitope screening techniques are. Relatively fewer antigen candidates for *A. baumannii* have been found and made accessible for vaccine development than other infections. On the other hand, the development of novel antigen candidates is probably going to happen more quickly now that *A. baumannii* research has exploded and we know more about the pathogen's virulence factors and molecular pathogenesis. Furthermore, two more epidemiological findings on the serotype prevalence of clinical *A. baumannii* separates are crucial for the logical design of glycoconjugate vaccines with broad serotype coverage, even though it was acknowledged that a vaccine targeting even a small number of *A. baumannii* strains may still be beneficial.

Therefore, given the current state of vaccine development technology, which includes reverse vaccinology, immunoproteomics, glycomics, and other innovations, there is a good chance that within the next five to ten years, multicomponent *A. baumannii* vaccines with well-defined compositions, high-efficacies, wide coverage, and favorable safety profiles will be put through clinical trials.

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Author contributions

Conceptualization, design and writing of the manuscript: Eskandar Hoseinnzhad Lazarjani.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent to publication

Not applicable.

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Application of Artificial Intelligence in Cancer Management with a Personalized Medicine Approach

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Abstract

Recently, the medical profession has seen an accelerated integration of devices equipped with artificial intelligence (AI) technology, thanks to significant advancements in this area. Over 60 medical devices integrated with AI have already received approval from the Food and Drug Administration (FDA) in the United States. The widespread use of AI technology in medicine is seen as an unavoidable trend soon. AI technology is now being used in the area of cancer, particularly in radiology, for clinical use of medical equipment. It is anticipated that AI technology will become a crucial core technology in this industry. Precision medicine, which involves selecting the most suitable treatment for each patient based on extensive medical data like genome information, has gained global popularity. AI technology is anticipated to play a crucial role in extracting valuable data from vast medical datasets and applying it to medical care. Cancer is the second most prevalent global illness that relies on oncogenic mutations and non-mutated genes for its survival. The significant variability of tumors may result in varying curative results when using the same medications or surgical procedures in people with the same tumor. This highlights the need for more precise treatment approaches for tumors and personalized therapies tailored to individual patients. We summarize current and noteworthy AI advances in cancer research in this report. We also discuss AI's limitations, challenges, and potential effects on cancer therapy. We also explored AI in omics, pathology, and medical imaging.

Keywords: Artificial intelligence, Cancer therapy, Precision medicine, Machine learning.

Introduction

Cancer poses a significant risk to human well-being, resulting in a substantial number of deaths and an increasing occurrence rate. Early diagnosis and treatment may lead to the successful cure of several forms of cancer. Nevertheless, the current state of cancer therapy is suboptimal. The death rates for cancer, particularly prostate, colorectal, and cervical cancer, are persistently high and are still increasing (1). These tumors have no reliable means for screening and therapy, leading to patients not receiving prompt and effective treatment. Furthermore, tumors exhibit a significant degree of heterogeneity, posing considerable obstacles in their management. Hence, there is a want for novel diagnostic and therapeutic approaches that are customized to suit the specific

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needs of each patient (2).

Precision medicine (PM) is an auspicious methodology that considers a person's genetics, environment, and habits, with a focus on elucidating, identifying, and addressing diseases. It aims to develop a personalized treatment plan for patients by gathering multi-omics or multi-mode information from individuals. Moreover, artificial intelligence (AI) employs computers or robots to execute tasks by imitating or replicating human intellect, primarily via machine learning (ML) and deep learning (DL) (3). Artificial intelligence can analyse a vast quantity of data to facilitate the groundbreaking discovery of PM. Artificial intelligence has shown exceptional capabilities in efficiently processing, extracting valuable insights from, and comprehensively analyzing data. It may use this data to create various models that contribute to the attainment of project management objectives (3).

The term "artificial intelligence" was first used at the Dartmouth Summer Workshop in 1956, when it was often referred to as "thinking machines. AI may be described as the capacity of a computer to acquire knowledge and identify patterns and connections via a sufficient number of representative instances (4). It then applies this information successfully to make decisions when faced with unfamiliar data. AI is a broad concept that includes and is often used interchangeably with, machine learning and deep learning. Machine learning is a branch of AI, whereas deep learning is a specific subset of machine learning that emphasizes the usage of deep artificial neural networks. These neural networks include numerous completely hidden layers (4). Deep learning has been more popular in recent years because of its remarkable achievements in computer vision applications, including face recognition and picture categorization. The versatility of deep learning has expanded its potential applications in cancer research and medicine. It can effectively and precisely identify cancer from stained tumor slides or radiology images, offering the possibility of relieving pathologists and radiologists from monotonous and repetitive duties (4).

Tumors are often detected in two scenarios: one is via screening of high-risk populations. Another aspect is the identification of tumors that exhibit clinical symptoms. Once cancer is found, patients will have further exams, including a physical examination, imaging tests, pathology analysis, and serum tumor marker testing. These discoveries will enable precise diagnosis, staging, and classification of tumors, hence facilitating precision therapy for the patient's benefit (5). AI may contribute to several aspects of tumor management, including prevention, screening, diagnosis, therapy, and prognosis prediction. Once AI is integrated into the clinical process, it will enhance the accuracy of lesion identification and optimize the screening procedure. Furthermore, AI may enhance the accuracy of medical diagnosis by assisting clinicians in differentiating between genuine and erroneous illness development. Ultimately, artificial intelligence can assess the benefits and drawbacks of various treatment plans and provide the most optimal course of therapy for patients (5).

NGS technology has led to the accumulation of omics data, including genomes, proteomics, and transcriptomics. Simultaneously, the substantial expansion and extensive accessibility of patients' health data, including electronic medical records, clinical trial information, and medical pictures, have ushered in the era of "big data". The most effective technique of analysis is using AI to analyze data, since ML and DL algorithms may uncover hidden patterns, significant information, and relevant knowledge within the data. The disease-related information is gathered by the extraction of data, which aids in clinical analysis. ML and DL may be used to analyze omics data for many purposes such as creating models, identifying markers for assessment, classification, and outlook, detecting molecular changes in DNA, RNA, and protein, predicting medication effectiveness and treatment response, and developing specific pharmaceuticals (6, 7).

In recent years, a significant amount of research has used DL techniques in the fields of cancer detection, precision medicine, radiation, and cancer research. Furthermore, the American Food and Drug Administration (FDA) has granted permission to many AI algorithms about cancer. In addition, the FDA released a fast-track approval strategy for AI medical algorithms in 2018 (8). In this study, we provide a comprehensive summary of the recent and significant advancements in the use of AI in the field of cancer. In addition, we emphasize the constraints, difficulties, and prospective consequences of using AI technology in cancer treatment. In addition, we discussed the use of AI in the field of omics, followed by its application in pathology and medical imaging. We elaborated on how these applications contribute to the advancement of precision medicine.

A brief introduction to AI in the field of cancer

The identification and cancer screening

Cancer screening has had a role in reducing the death rate of several prevalent malignancies. Notable instances of success include the detection of precancerous abnormalities such as cervical intra-epithelial neoplasia (CIN) for cervical cancer screening and adenomatous polyps for colorectal cancer screening. Treating these abnormalities results in a reduction in the occurrence of invasive cancer. Automation has been employed to enhance the effectiveness of cancer screening due to the need for high throughput technologies and rapid

turnaround (9).

Wentzensen et al. created a deep learning classifier to screen for cervical cancer using p16/Ki-67 dual-stained cytology slides. The classifier was trained using biopsy-based gold standards. During independent testing, AI-driven data science (DS) demonstrated equivalent sensitivity and much greater specificity when compared to both Pap smear and manual interpretation of DS. Significantly, AI-DS techniques decreased the number of unnecessary colposcopies by 33% compared to Pap smears (41.9% vs. 60.1%, $P < 0.001$). Furthermore, it demonstrated comparable effectiveness in detecting high-grade CIN, a condition that requires rapid treatment. A prospective randomized controlled trial involving 1,058 patients demonstrated that AI-assisted colonoscopy resulted in significantly higher rates of detecting adenomas and the average number of adenomas per patient compared to conventional colonoscopy (29.1% vs. 20.3%) (10). This improvement was primarily due to the identification of a greater number of small adenomas. It is crucial to note that a mere 1% rise in the adenoma detection rate is linked to a significant 3% decrease in the occurrence of colorectal cancer (11).

There has been considerable interest in using automated methods to identify and classify nodules on low-dose computed tomography (CT) and mammography for screening for lung and breast cancer. Various CNN-based models have shown classification accuracies ranging from 80% to 95%, indicating their significant promise in the field of lung cancer screening. Ardila et al. introduced a deep learning system that utilizes both the present and previous low-dose CT scans of patients to accurately forecast the likelihood of developing lung cancer. The approach achieved exceptional outcomes, with an area under the curve (AUC) of the receiver operating characteristic equal to 0.944. The efficacy of AI mammography in enhancing breast cancer screening has been confirmed in both preclinical and clinical investigations (12). McKinney et al. developed an AI system for detecting breast cancer by using a combination of three convolutional neural network (CNN) models. An improvement in the accuracy of diagnoses was demonstrated when comparing the original choices made during clinical practice with a decrease in both false positives and false negatives. According to a self-directed investigation conducted by six radiologists, the AI system demonstrated an Area Under the Curve (AUC) that was 11.5% greater than the average AUC attained by the six radiologists. Significantly, this AI system can extrapolate from the training data to multicenter data (13).

A promising field for the early identification of tumours is liquid biopsies, which analyse circulating tumour DNA (ctDNA) or cell-free DNA (cfDNA) collected by a simple blood test. These are especially crucial for cancer forms that presently lack an efficient screening approach. Cohen et al (14). conducted a study where they created CancerSEEK, a method for early detection and prediction of eight forms of cancer using ctDNA. The CancerSEEK method first categorises samples as cancer-positive by using a logistic regression model that analyses 16 gene mutations and the expression levels of 8 plasma proteins. A random forest classifier is used to predict the kind of cancer, with accuracies between 39% and 84%. While liquid biopsies show potential for early cancer diagnosis, their use has been restricted to conventional machine-learning techniques. With the growing use of liquid biopsies to gather data, we expect that DL models will remove the need for human selection and organization of distinguishing characteristics. Additionally, DL models will enable the integration of various kinds of data to improve the early identification of cancer (15).

Diagnosis, categorization, and assessment of cancer

There have been numerous reports on CNN-based deep learning models that can effectively diagnose cancers, classify different types of cancer, and determine the severity of cancer using histopathology (such as whole slide imaging [WSI]), radiology (such as CT and magnetic resonance imaging [MRI]), and endoscopy images (such as esophagogastroduodenoscopy and colonoscopy). These models have been found to achieve accuracies that are at least comparable to those of medical professionals (16). CNN-based DL models have shown remarkable accuracy in detecting malignant tumors from histopathology slides for the identification of cancer. The CAMELYON16 international competition aimed to diagnose breast cancer metastasis in lymph nodes using WSI with hematoxylin-eosin (HE) staining (17). The top-performing CNN algorithm, which was based on the GoogLeNet architecture, achieved an AUC of 0.994. This outperformed the best pathologist, who achieved an AUC of 0.884 and did so in a more time-efficient manner. Deep learning algorithms have also been used to forecast the source of unidentified primary tumors, a very demanding task in cancer diagnostics (18).

DL has repeatedly shown success in diagnosing malignant disorders with the use of CT, MRI, PET-CT scans, and endoscopy (19). In a recent study, Yuan et al. utilized CT scans to create a classifier using a three-dimensional (3D) ResNet algorithm. The purpose was to predict occult peritoneal metastasis in colorectal cancer. The classifier achieved an AUC of 0.922, which was significantly higher than the AUC of 0.791 obtained through routine contrast-enhanced CT diagnosis (20). Ke et al. used MRI data

from 4,100 patients diagnosed with nasopharyngeal carcinoma (NPC) to develop and evaluate a self-constrained 3D DenseNet model. The purpose was to accurately differentiate between NPC and benign nasopharyngeal hyperplasia. The model achieved an AUC of 0.95-0.97, indicating high performance (21).

In a multicenter investigation, Luo et al. created a gastrointestinal AI diagnostic system (GRAIDS) for the detection of upper gastrointestinal tumors using a CNN-based model. They then conducted a prospective study comprising six different graded hospitals to evaluate the system. The diagnostic accuracies ranged from 0.915 to 0.977 across the six hospitals. These accuracies were comparable to those of specialist endoscopists and better than those of non-experts. This suggests that community-based hospitals can enhance diagnostic efficacy. Overall, if their effectiveness is validated in multicenter prospective trials, these models might significantly enhance the accuracy of cancer detection, particularly in rural hospitals that have limited access to specialists (22).

In addition to dichotomous diagnosis, DL models are utilised for more complex cancer groupings and grading activities. Coudray et al. created DeepPATH, a model based on the Inception-v3 architecture, to categorise whole slide images (WSI) of lung tissues into three classes: normal, lung adenocarcinoma, and lung squamous cell carcinoma. The model achieved an AUC of 0.97. The CNN was effectively taught to automatically execute the Gleason grading of prostate cancer, achieving a 75% concordance between the algorithm and pathologists. Radiology scans may also be used for cancer grading (23). Zhou et al. devised a deep learning methodology, using SENet and DenseNet, to forecast the grades of liver cancer (low vs high) by analysing MRI images. The reported AUC for this strategy was 0.83. Collectively, these studies demonstrate the encouraging use of artificial intelligence in the classification and assessment of cancer, with comparable results to those of highly skilled professionals (24).

Anticipating genetic alterations in cancer

Deep learning algorithms have also been used to analyze histopathology photos to identify and describe the genetic and epigenetic variations present. A Convolutional Neural Network (CNN) was trained to predict six distinct genetic mutations in lung cancer using Haematoxylin and Eosin (HE) stained WSI (23). The performance of the model was evaluated on a separate testing cohort, yielding AUC values ranging from 0.733 to 0.856. The use of WSI allowed the CNN model, namely Inception-V3, to accurately detect prevalent genetic alterations in liver cancer, achieving AUC values greater than 0.71. WSI has facilitated the development of DL techniques that can forecast various genetic alterations, including whole-genome duplications, chromosomal arm gains and losses, localized enhancements and eliminations and gene changes, across different types of cancer (25). DL models have been utilized for predicting mutational footprints, including microsatellite instability (MSI) status and tumor mutational burden (TMB) status. These footprints are crucial indicators for determining the effectiveness of checkpoint immunotherapy (25). In a recent study, Yamashita et al. used the MobileNetV2 architecture to develop a transfer learning model called MSINet. They trained and evaluated this model to identify the MSI status in HE-stained WSI in a sample of 100 primary tumors from colorectal cancer patients. The researchers obtained an impressive AUC of 0.93 for the model (26).

Cao et al. used many examples of learning-based deep learning to classify the MSI condition in a colorectal cancer population using WSI. They successfully reached an AUC of 0.85 (27). Wang et al. conducted a study to categorise TMB status using WSI. They evaluated eight different DL models and found that GoogLeNet performed the best for stomach tumors with an AUC of 0.75, while VGG-19 was the top performer for colon cancer with an AUC of 0.82. The findings suggest that characteristics extracted from histopathology pictures may serve as predictors of genetic mutations in situations when it is not feasible to get tumor samples for mutation screening. Significantly, it might be more economical than direct sequencing (28).

Artificial intelligence big data helps PM manage malignancies

Big data technology primarily encompasses the processes of data analysis, data mining, and data exchange. The potential impact of this technology on cancer diagnosis, treatment, prevention, and prognosis is groundbreaking. However, the process of converting data into useful information for the benefit of patients is now experiencing a significant slowdown. One of the main causes for this is the substantial delay in data analysis compared to data creation (29). Almost every element of tumor research has been impacted by the changes brought about by “big data”. For instance, the technology may use data from NGS to identify frequently mutated genes, aberrant gene expression, and biomarkers in tumors. This enables precise diagnosis and prediction of prognosis, as well as the identification of the underlying cause of a disease. Additionally, it facilitates the development of targeted medications for effective therapy (30).

The equipment can evaluate both visible and invisible aspects in medical pictures, and extract and refine these characteristics to get data about

evaluation, therapy, and prediction. Furthermore, the technology can examine patients' demographic and medical data, together with result data, to forecast the elements that influence the prognosis of cancer patients (31). Furthermore, AI is employed to examine, extract, and manipulate tumor-related information, construct a healthcare provider platform using a substantial amount of tumor-related data, effectively address the challenge of complex medical therapy for patients, and minimize the wasteful utilization of medical resources. The potential of big data reanalysis has not been fully exploited so far, but we cannot disregard its significance. It can analyze the data inside a pre-existing database and provide novel insights. For instance, Borziak et al. identified the dedifferentiation indicators of liver cancer by using data from pre-existing datasets.

Big data innovation is primarily employed in particular domains, including omics, pathological imaging, and medical imaging (32). Nevertheless, it fails to integrate data from many domains for data analysis, mining, and sharing, resulting in incomplete utilization of data and failure to fulfil the requirements of physicians and patients. Combining omics and non-omics information may help solve the obstacles associated with diagnosing, treating, and monitoring cancer. AI is valuable for analyzing complex and diverse high-dimensional data sets, particularly in the fields of multi-omics, intergroup methods, and data integration. This enables the identification of cancer molecular mechanisms and the discovery of new diagnostic and prognostic indicators, leading to more precise treatment for cancer (33).

AI aids cancer PM in omics

The vast volume of data resources produced by NGS may provide crucial insights into tumors. Integrating AI with the available data will aid in elucidating the causes and development of tumors, as well as facilitating precise diagnosis, risk assessment, and study of different subtypes of the illness (33, 34). In addition, AI can identify novel therapeutic targets, assess the effectiveness and resistance of anticancer medications, create new targeted drugs, enhance cancer immunotherapy, monitor tumor recurrence and progression, uncover new biomarkers, and forecast the prognosis and survival analysis of patients with tumors. AI facilitates precision medicine for cancer patients, effectively bridging the gap between omics data and clinical practice. Due to the high-dimensional and complex nature of the data produced by NGS, cancer detection techniques using NGS often need comprehensive coverage of higher-dimensional and deeper-seated data. This is done to increase the chances of identifying a small number of mutations in tumor cells and to raise the sensitivity and accuracy of AI algorithms (35).

AI supports tumor PM in genomics

Genomics, a field that utilizes nucleotide sequences for data processing, has increasingly integrated with clinical practice in recent years. The substantial aggregation of data has enhanced the comprehension of cancer susceptibility and has empowered us to progressively predict discernible therapeutic outcomes for tumor sufferers (36). Utilizing spatial and single-cell genomics may help rebuild the process of carcinogenesis, leading to a more thorough knowledge of tumors, clarifying the ambiguous etiology in humans, and enabling the development of targeted therapies based on this mechanism. The integration of machine learning (ML) with genomics data may facilitate the identification of cancer subtypes, the identification of novel markers and therapeutic targets, and the enhanced comprehension of cancer-causing genes (37, 38). This, in turn, enables the provision of personalized therapy for patients. Wang et al. created a complex deep network model that combines image-genomics data to detect different forms of lung cancer. This model also uses attention weights to assist biomedical specialists in identifying prospective therapy targets (39). Furthermore, Vanderbilt et al. devised and verified a novel method to detect DNA viruses from matched normal or tumor NGS samples and investigate the association between viruses and tumor types without the need for further sequencing. Information on these viruses may be used for the diagnosis and treatment of people with tumors. Their investigation demonstrated the role of DNA viruses in the development of tumors (40). Sudhakar et al. used cancer genomics data to construct a pan-cancer model to predict and discover novel driver genes. Identifying driving genes is crucial for comprehending the process of carcinogenesis and developing treatment methods since it has significant biological and therapeutic implications (41).

AI helps PM for cancers in transcriptomics

Transcriptomics is a potent method for assessing all the transcripts generated during metabolism. Transcriptomics has enhanced our understanding of malignancy by providing insights into its incidence, development, tumor microenvironment, and immune-oncology (42). It enables the direct measurement of gene expression levels and analysis of the activation of relevant biochemical pathways. Transcriptomics serves as a connection between genomics and proteomics, primarily using quantitative reverse-transcription-polymerase chain reactions, microarrays, and NGS (43). RNA sequencing is widely regarded as the premier method for high-throughput gene expression assessment due to its superior accuracy in quantifying gene expression (43). Data extraction or advanced mathematical techniques,

such as ML or DL, are used to extract features that aid in cancer evaluation as well as initial diagnosis. These methods also help identify new or previously unknown cancer markers and possible targets for therapy. Additionally, they assist in prioritising drugs and predicting cancer drug sensitivity and prognosis (43). Warnat-Herresthal et al. showed that machine learning-based transcriptomics may aid in the identification of acute myeloid leukaemia (44). Furthermore, Ben Azzouz et al. used a machine learning methodology using transcriptomics data to determine the subtypes of triple-negative breast cancer. This strategy was implemented to address the challenge of heterogeneity in the management of the illness. ML-based transcriptomics have been utilized to identify predictive biomarkers for prostate cancer, diagnose colorectal cancer, and predict the immune reaction (45).

AI supports cancer PM in proteomics

Proteomics offers extensive and precise data on proteins in organs, bloodstream, and cell specimens. Proteomics and machine learning-based profile evaluation may provide protein expression profiles that are more precise and responsive in identifying protein biomarkers compared to conventional single-omics approaches (46). These molecules can diagnose cancer, forecast prognosis, uncover crucial signalling pathways involved in disease processes, identify novel targets for therapy, assess the effectiveness and toxicity of pharmacological treatments, and predict therapeutic responses, recurrence, and metastasis. Henry et al. have introduced a technique for medication ranking that uses machine learning to forecast drug response based on proteomics data. This approach prioritises pharmaceuticals to choose the most appropriate one for each patient. Furthermore, Federica et al. developed a more explicit and easily understandable Decision Support System (DSS) to aid in the diagnosis of high-grade serous ovarian cancer. Hence, the use of AI-driven proteomics is likely to have a significant impact on the precise identification and management of tumors in the next years (47, 48).

In addition to the aforementioned commonly used omics data, additional types of omics data such as metabolomics, immunomics, and microbiome data are also employed. For example, using AI to dispose of metabolomics data might aid in diagnosing and evaluating therapy response, discovering novel biomarkers, and determining patient tolerance and cancer status (whether it is invasive or non-invasive). Furthermore, the AI model using immunomics data can predict the urgent immunological features of individuals with cancer (49-52).

Drug design in cancer via ML

The process of drug creation is both expensive and time-consuming, sometimes spanning a duration of up to 15 years. The creation of the pipeline starts with the first phase 0, which involves basic studies or identifying drugs. Phase I, phase II, and Phase III are clinical studies, while Phase IV involves pharmacovigilance research. Phase I is investigating the relationship between dosage, toxicity, and short-term adverse effects (53). In contrast, phase II and Phase III are dedicated to evaluating the effectiveness of the medicine by comparing it to established treatments for the specific condition under research. The purpose of Phase IV is to closely observe and assess any enduring adverse effects of the medication. The primary obstacle encountered in the medication development process is the substantial rate of failure and subsequent financial detriment throughout the concluding phases of development (53).

Thanks to the recent progress in AI technologies and machine learning approaches, we can now accelerate creation and decrease the chances of error. Machine learning models, including support vector machines, random forests, Bayes' theorem, and others, are used at every step of drug discovery to make precise predictions and gain valuable insights. Scientists working in the area of cancer treatment development are increasingly using the Bayesian method as a strategy (54). Bayesian approaches provide a seamless solution for addressing case fatality, survival analysis, dropouts from clinical studies, and difficult computing challenges. In the age of vast information, the Bayesian statistical technique is more appropriate for merging the existing data with prior knowledge and generating posterior probability for both the efficacy and safety of medicine (54).

Bayesian statistics may be used at several stages of the research process, including planning, trial actions, analysis, post-marketing surveillance, and meta-analysis. A novel technique called Bayesian Analysis to identify Drug Interaction Targets (BANDIT) has been created. BANDIT utilizes an integrated big data approach to predict drug targets, validate them for clinical development, and explore medication repurposing. This machine-learning algorithm discovered a new substance that inhibits microtubules and is effective against breast cancer cells that are resistant to all existing officially licensed medications targeting microtubules. The Bayesian adaptive design may also be used in phase I oncology trials, which are carried out in a limited patient population to ascertain the maximum tolerable dosage (MTD) of the therapeutic compound (55).

A multicenter and non-randomized Bayesian adaptive design research was done to evaluate the security and to identify the suggested dosage of the combination therapy of the γ-secretase inhibitor MK-0752 and gemcitabine for individuals with pancreatic

ductal adenocarcinoma. The research accomplished these objectives. Yan et al. introduced a Bayesian keyboard decision approach that utilises the posterior distribution of the toxicity probability to accurately determine the genuine MTD. Oncology medication development often includes a proof-of-concept study (PoC) conducted towards the conclusion of the phase I or phase II trial (56). PoC research is conducted to gather preliminary evidence of the therapeutic effectiveness by using a limited number of patients. By using a Bayesian framework, decision-making in PoC may be enhanced since it allows for the direct estimate of data on the desired outcome. The Bayesian design can reduce the length of a cancer clinical trial by combining the phase II/III studies into a single validation trial. A new adaptive shrinking approach called ComPAS was recently created utilising Bayesian model selection and hierarchical methodologies. This technique enables the removal of unsuccessful medications and the incorporation of novel combinations into existing clinical pipelines, using accumulated trial data in an adaptable and seamless manner (56).

While the Bayesian technique has shown to be efficient in all stages of drug development in cancer, it is also accompanied by many obstacles. Applying the Bayesian technique necessitates making decisions on prior knowledge, trial-derived information, and the mathematical model to be used, right from the outset of the design phase. Modifications in the initial data and the accuracy of the information during a subsequent phase might potentially impact the scientific integrity of the study findings (57). There is a proposal to establish the appropriate statistical analysis method for cancer clinical trials at an earlier stage. The Bayesian adaptive design may be affected by operational biases, hence it is crucial to ensure the secrecy of the data. Recent progress in machine learning techniques and increased computer performance have enabled the execution of computations for intricate Bayesian models. Moreover, the use of machine learning techniques and statistical instruments in drug development pipelines has the potential to reduce the expenses and duration of drug development, while also advancing the progress of precision medicine for cancer therapy (57).

Challenges

AI technology's significance has gained global recognition, leading numerous nations to actively promote AI research as a part of their national policies. Given its immense potential, there are elevated anticipations for AI technology, and AI technology will probably be progressively integrated into the area of cancer in the next years. Although AI technology has immense promise, there are still certain obstacles that must be addressed. Thus, we have outlined the primary obstacles that must be consistently addressed.

Overfitting

Overfitting refers to a situation in machine learning where a model becomes too specialised to the training data and performs poorly on new, unseen data. In the context of machine learning and deep learning approaches, overfitting occurs when the training error is low, but the generalization error (the mistake in predicting unknown data) is high. Especially in the medical area, where there is a limited quantity of training data, it is always important to carefully assess the ability of the developed model to apply its knowledge to new situations. Validation is crucial when seeking to clinically integrate medical devices with AI. It is necessary to meticulously check the overall performance of these devices via clinical studies, surpassing the level of scrutiny applied to traditional medical equipment.

Black box problem

Due to the intricate nature of the analysis process involved in machine learning and deep learning approaches, a black box issue emerges wherein people are unable to comprehend the analysis process of the generated findings. The inclusion of an opaque component in the system poses challenges for both the designer and user in accurately anticipating the system's behaviour throughout the design and use stages, hence impeding the system's safety. The General Data Protection Regulation (GDPR), implemented in May 2018, mandates transparency of AI under Article 22 in Europe. Therefore, it is imperative to solve the problem of black box to comply with GDPR. Three primary methodologies are often used to enhance the interpretability of ML and DL (58).

Discrepancies across facilities, particularly in healthcare imaging

Medical imaging analysis is susceptible to variations in facility characteristics, such as the use of different manufacturers and models of devices, variations in protocols, and differences in operators. Several studies, including our own, have observed that the accuracy of predicting data from one facility using a trainer built on data from another facility is significantly diminished. This issue is often referred to as the domain shift problem, and it is a crucial matter that must be addressed to advance the field of medical AI (58).

Conclusion

Artificial intelligence has shown encouraging outcomes in several domains of oncology, such as

tumor screening, identification, diagnosis, therapy, and prognosis forecasting. As AI advances and computer performance improves, along with the rapid growth of data, new learning methods like hybrid learning will continue to emerge. These methods will enhance the overall performance of models by enabling efficient data analysis and accurate prediction. The newest machine learning and deep learning model, capable of analyzing diverse datasets, will enhance the potential of project management. To summarize, AI-supported precision medicine may aid in the early detection, diagnosis, and treatment of cancer. Additionally, it can assist in determining the most effective treatment plan, thereby enhancing patient prognosis and treatment outcomes.

Authors' Contribution

Yasam Vojgani and Mohadeseh Sadeghinia were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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Application of Cytokines and Growth Factors in Immunotherapy

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Abstract

The main goal in cancer treatment is to eliminate tumor cells with minimal harm to healthy tissue. The immune system is ideal for this task as it can identify and eliminate abnormal cells while providing long-term defense against recurrence. Various immune-based cancer treatments activate the immune system or help cancer cells recognize and activate immune cells within the tumor. Immunoregulatory cytokines play a crucial role in treating immune disorders. They regulate macrophage degradation of antigens and promote cellular functions. Lymphocyte interactions can lead to immune cell maturation, while other products limit lymphocyte activation. Cytokines are categorized as interleukins, growth factors, interferons, and colony-stimulating factors. Soluble proteins known as cytokines are essential for mediating and regulating cell interactions in various parts of the body, including the nervous system, gut, and bone remodeling. The study of cytokines' structure and function has proven incredibly beneficial for both immunology and commercial research. By understanding the different domains and analogues of cytokines, researchers have gained important knowledge about how these proteins bind to receptors. Moreover, identifying similarities between various cytokines has offered valuable insights into the workings of cytokine receptors. Understanding the mechanisms behind immunotherapy resistance is important to identify new therapeutic targets. By investigating these pathways, researchers can develop innovative strategies to overcome resistance and improve treatment outcomes. Combining therapeutic modalities to target multiple aspects of the tumor microenvironment simultaneously can overcome the limitations of individual treatments and improve antitumor response. Understanding resistance mechanisms to immunotherapies can lead to the development of tailored strategies to combat treatment resistance and maximize treatment response.

Keywords: Cytokine, Cancer, Immunotherapy, tumor vaccine.

Overview of Immunotherapy in Cancer Treatment

Cancer is one of the deadliest diseases that humans face. At present, surgeons remove tumor tissue from patients and then patients receive chemotherapy and radiotherapy (1). After these three approaches to tumor treatment, many patients relapse due to residual tumor tissue. In addition, chemotherapy and radiotherapy tend to have systemic toxicity. In

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general, the main causes of disease recurrence are ineffective anti-tumor immunity and inefficiently activated immune system cells (2). Recent years have seen significant progress in understanding how various types of cells respond to different pro-inflammatory cytokines. This understanding has been greatly aided by the measurement of signal-transduction pathway activation, gene expression patterns, and cellular functional responses. While much attention has been given to the activities of pro-inflammatory cytokines, new evidence has emerged showing that other 'suppressive' cytokines can also activate important signaling pathways like NF-kB, MAPK, and STAT (3, 4). This complexity makes it challenging to fully grasp how cells respond to different cytokines, especially when considering the different timeframes over which these responses occur (5). For example, acute-phase pro-inflammatory cytokines can rapidly affect gene expression, while the resolution of inflammation happens much later. The intricate cellular responses to pro-inflammatory cytokines are illustrated through the activation of pathways like NF-kB (6). After treatment with these cytokines, NF-kB is activated through a series of interactions and phosphorylation events, ultimately leading to the regulation of cellular activities (7, 8).

Immunotherapy is a treatment that employs the host immune system to recognize and eliminate cancer cells more effectively than it could do unaided. Tumor immunotherapy aims to enhance anti-tumor immunity by the administration of cytokines, immune checkpoint inhibitors, adoptive cell transfer, and other types of treatment. Recently, tumor vaccines have also been employed in tumor immunotherapy. Many excellent cytokines and growth factors can be used as adjuvants in tumor immunotherapy to enhance the anti-tumor immune response (9).

Types of Cytokines and Growth Factors

Cytokines are small-molecular-weight proteins and glycoproteins that are produced by many types of cells such as fibroblasts, endothelial cells, macrophages, T-lymphocytes, etc. They are produced by virtually all nucleated cells. Interleukins, lymphokines, and monokines are types of cytokines. They can be classified as proteins, glycoproteins, and peptides. Cytokines are regarded as vital soluble mediators of the immune system and inflammatory response to infection, trauma, and inflammation. They are produced by many cell types to combat stress and infection (10). It is indeed a balance of pro-inflammatory, anti-inflammatory cytokines, and other factors that underlie the dynamics of the physiological response to stress and disease. Cytokine action is complex with redundancy of action, and one cytokine may have different effects on different cells, depending on the state of activation of the responding cell. Many cytokines have been identified which possess activational, chemoattractant, metabolic, and proliferative properties essential for the regulation of host responses (11).

Cytokines can be classified by function, target cells, time of action, source, type of effect, or structure. A classification scheme collects together under broad categories several different, but related, terms. Some classification schemes are simple, making it easy to group cytokines, but arbitrary in that the influence of the structure on the function may not be obvious. Others are more complicated but take account of more than just the structure (12).

Cytokines impact the function of a variety of tissues, act directly at a target site, locally control the immune response, control gene transcriptions, autocrine and paracrine signaling, and, in addition, cytokines are responsible for the control of lymphocyte activation and tissue injury (13). This class of molecules includes various interleukins, colony-stimulating factors, interferons, and tumor necrosis factors (14). Responses to cytokines are mediated by specific receptors present in target cells. Cytokines such as tumor necrosis factor and interleukins have effects on endothelial cells which are important in the regulation of angiogenesis (15, 16). Indirectly, interleukins and other cytokines have immunosuppressant functions, engaging in lymphocyte regulation. Many cytokines are pleiotropic, influencing a wide range of target cells and systems (17, 18). Cytokines were initially identified for their role in inflammation, but their biological effects are now known to be much broader. Nowadays, the role of cytokines is also recognized in health and disease (19, 20). Cytokines have untoward effects and their role in the expansion of inflammatory and autoimmune diseases is discussed. In addition, cytokines are attracting interest in their potential use in diagnostics, prognostics, and as therapeutic agents (21, 22).

Using anti-tumor immunity to treat cancer patients is not a new idea. The most common type of immunotherapy has been to induce a tumor-specific immune response using immunogens (23). Surgical tumor resection and chemotherapy, in effect, remove the chloroplast but leave spores when administering cocktails of cytokines and other immunostimulatory compounds to induce a tumor relapse (24, 25). These immunostimulatory cytokines include GM-CSF, IL-2, IL-15, IL-21, and IFN-γ (26). These immune-stimulating cytokines can enhance dendritic cell maturation, activate T cell proliferation and survival in vivo, trigger natural killer cell activation, and increase the number of dendritic cells (27). Adoptive cell transfer and immune checkpoint inhibition are also two types of active immunotherapy. In addition, some immune-stimulatory cytokines have also been found to mediate tumor outcomes (25, 28).

Role of Cytokines and Growth Factors in Cancer Immunotherapy

In recent years, it has realized the pivotal role of the immune system in cancer. This has led to new therapeutic opportunities, using cytokines and antibodies to target antigens. Success with monoclonal antibodies targeting CTLA-4 and PD-1 has opened doors for effective treatment (29). However, challenges remain in regulating the immune response without harming healthy tissues. To address these challenges, we need to explore the mechanisms that influence immune cell populations (20, 30). Understanding these interactions can unlock novel strategies for targeted therapies (31). Additionally, research is focused on understanding the balance between immune activation and regulation to minimize adverse effects. This approach has the potential to revolutionize cancer immunotherapy, providing hope to patients and improving outcomes (32, 33).

Current Immunotherapeutic Approaches

Immunotherapy for cancer can be achieved through a variety of methods, including cytokines, growth factors, monoclonal antibodies, adoptive transfer of immune effector cells, vaccines, and gene transfer (34). At present, cytokines and monoclonal antibodies have been the most successful in treating the disease, helping thousands of patients (35). Cytokines such as interleukins, interferons, and colony-stimulating factors can boost a patient's immune response, while monoclonal antibodies directly target cancer cells by identifying tumor antigens (36). Overall, immunotherapy has become an important treatment for various diseases involving infectious agents or abnormal cells, with key players including interferons, interleukins, monoclonal antibodies, immune effector cells, and hematopoietic growth factors (37). Other immune system mediators, like tumor necrosis factors and transforming growth factors, are also likely to play a significant role as therapeutic agents (38, 39).

Autoimmune Diseases and Cytokine Therapy

Autoimmune diseases are long-term illnesses that occur when the body's immune system mistakenly attacks its antigens, leading to tissue damage. These diseases can affect various parts of the body, such as glands, bones, blood, and skin (40). The first recorded case of autoimmunity in humans dates back to ancient Egypt, with diabetes mellitus being the classic example. However, evidence suggests that other civilizations, including the ancient Greeks, Romans, and Chinese, also experienced autoimmune diseases (41). Globally, the prevalence of AID is estimated to be around 5-15%, with conditions like systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, alopecia areata, and mucosal lichen being some of the most common. Genetic factors play a role in the development of autoimmune diseases, but environmental influences and other non-genetic mechanisms also contribute (42). The pathophysiology of AID involves a wide range of cells and molecules, with immune and non-immune cells and cytokine secretions all playing a role. Recently, the composition of the microbiota has also been identified as a potential factor in the development of autoimmune diseases, but further research is needed to better understand this connection (43, 44).

Cytokine-Based Therapies

Cytokines are prescription drugs that have a relatively short lifespan in the body, typically lasting only minutes, or in some cases, a few hours. Despite their brief existence, they are constantly being produced by our cells to maintain circulating levels and ensure proper immune system function (45). These tiny protein molecules play a vital role in regulating various cell activities, from controlling the development of secondary sex characteristics to influencing T cell lymphoproliferation and suppressing certain cytokines that may cause inflammation (46). Due to their immense importance in maintaining homeostasis and promoting optimal immune responses, the biotechnical and pharmaceutical industries have taken a keen interest in targeting cytokine activities for potential therapeutic interventions (47).

The goal is to develop cytokine-based drugs that can specifically modulate and regulate immune responses, providing targeted treatment options for various diseases. In recent years, significant progress has been made in the development of cytokine-based drugs for the management of chronic inflammation-associated diseases. These diseases, such as asthma, atopy, rheumatoid arthritis, and sepsis, pose significant challenges to patients and healthcare providers alike (48). However, with the introduction of cytokine-based drugs, there is renewed hope for effectively managing these conditions and improving the quality of life for millions of individuals worldwide. Clinical trials evaluating the efficacy of cytokine-based drugs in treating inflammation-associated diseases have shown promising results. These drugs have demonstrated their ability to modulate cytokine levels, dampen excessive immune responses, and alleviate symptoms associated with chronic inflammation (45).

By targeting specific cytokines that are known to contribute to disease progression, these drugs offer a more tailored and personalized approach to therapy. Moreover, the potential of cytokine-based drugs extends beyond their current applications. As researchers continue to elucidate the mechanisms

underlying various diseases, cytokines present themselves as candidates for further investigation and development as antigens for future treatments (49). By harnessing the unique properties of cytokines and leveraging their role in immune regulation, scientists may uncover new therapeutic avenues for an array of conditions (49). Cytokines are remarkable molecules that play a crucial role in regulating cell activities and immune responses. The development and utilization of cytokine-based drugs hold great promise for the treatment of chronic inflammation-associated diseases. With ongoing research and clinical trials, these drugs have the potential to revolutionize the field of medicine and pave the way for more targeted and effective treatments. Using the therapeutic power of cytokines, great progress has been made in the treatment of various diseases, ultimately improving the lives of many individuals (50).

Challenges and Future Directions

The use of cytokines in clinical treatments is rapidly expanding at an unprecedented rate. Cytokines, which are indispensable proteins utilized to regulate the body's immune system, play an indispensable and pivotal role in combating infections and infectious diseases such as cancer. Despite the remarkable progress that has been achieved thus far, it is imperative to acknowledge that there exists an untapped potential of immense magnitude when it comes to employing cytokines for therapeutic purposes (51, 52). It is of utmost importance to overcome the multitude of challenges that are associated with the therapeutic utilization of these incredible proteins, including but not limited to issues about their biological activity as well as their intricate pharmacological aspects (53).

With amazing advancements in technology, especially in recombinant protein technology and site-specific pegylation, cytokines can now be restructured for a variety of uses. Looking forward, the focus is on finding the most effective combination of cytokines and improving treatment programs (54). In addition, the combination of cytokines with other drugs and the use of delivery methods are expected to make significant progress. It is clear that the field of cytokine therapy has great potential for improvement and offers many opportunities to improve human health (55).

Limitations of Cytokine-Based Therapies

Although there is tremendous potential in current immunotherapies that aim to activate antitumor-specific responses, they also have a myriad of limitations. These limitations encompass a lack of response in the majority of patients, severe side effects that accompany treatment, the presence of immunosuppressive cells and molecules in the tumor environment, and the emergence of resistance to these efficacious therapies (56). To overcome these barriers and augment their effectiveness, innovative approaches or combinations of therapies need to be explored (57). A promising avenue for addressing these challenges lies in the development of novel drugs that specifically target immunosuppressive cells, molecules, or cytokines (58). This cutting-edge strategy offers a certain degree of hope for patients, as it holds the potential to unleash the full power of the immune system against tumors. However, it is imperative to acknowledge that simply increasing the dosage of the same agent does not guarantee success (59, 60). This traditional approach, though utilized in some cases, has its own set of limitations, particularly when it involves the administration of cytokines at remarkably high doses (61). Consequently, the scientific community is actively pursuing alternative strategies to enhance the efficacy of immunotherapies (62). One such approach involves combining different therapeutic modalities to create a synergistic effect that targets multiple aspects of the tumor microenvironment simultaneously (63). By doing so, it may be able to circumvent the limitations inherent to individual treatments and bolster the overall antitumor response. These innovative combinations of therapies have the potential to reshape the landscape of cancer treatment and improve patient outcomes (64, 65). Moreover, it is crucial to understand the underlying mechanisms that drive the resistance to immunotherapies. By unravelling these intricate pathways, researchers can identify novel targets for therapeutic interventions, thereby creating innovative ways to overcome resistance (66). This focus on understanding the molecular intricacies of tumor evasion mechanisms opens the door to the development of tailored strategies that effectively combat treatment resistance and maximize treatment response (67).

Conclusion

In conclusion, while there are inherent limitations in current immunotherapies, the scientific community is steadfast in its pursuit of overcoming these barriers. By exploring novel approaches, combining therapies, and unravelling resistance mechanisms, researchers offer a glimmer of hope for patients and open up new vistas in the fight against cancer. Through these diligent efforts, researchers strive to transform immunotherapies into formidable weapons against tumors, unlocking their true potential in eradicating cancer and improving the lives of countless individuals.

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Authors' Contribution

Mahnaz Saremi was involved in the conceptualization, design and review, Farnoosh Honarmand was involved in writing the manuscript draft. The authors read and confirmed the final manuscript.

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The Dual Role of Neutrophils in Cancer: with a Focus on Targeted Cancer Therapy

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Abstract

Neutrophils have gained significant interest in recent years due to their ability to promote malignancy. A high neutrophil-to-lymphocyte ratio is seen as a prognostic marker for cancer patients. Neutrophils are now recognized as immunological cells of the innate immune system that have several functions and are actively involved in the pathological process of cancer, rather than being just spectators. Their wide range of variations and adaptability are becoming more and more acknowledged. This review provides a concise overview of prior research investigating the functions and processes of neutrophils in the onset, advancement, spread, and recurrence of cancer. We provide a general overview of many studies that examine the characteristics and roles of neutrophils associated with tumors. Additionally, we discuss the formation of neutrophil extracellular traps, which are web-like structures produced by neutrophils that contribute to the advancement of cancer. Furthermore, we explore the interactions between neutrophils and the tumor microenvironment. Furthermore, several focused research on therapeutic neutrophils have achieved notable advancements and shown promising approaches for cancer therapy.

Keywords: Genomic analysis, Autoimmune disorders, Personalized medicine, Neutrophil.

Introduction

Neutrophils are a crucial component of the body's defences that react to infections and tissue injuries. In humans, they make up 50-70% of circulating white blood cells, whereas in mice, they account for 10-25%. Neutrophils are derived from the bone marrow granulocyte monocyte progenitor (GMP) and are discharged into the bloodstream as fully developed cells with a segmented nucleus. Neutrophils are immune cells that have a limited lifespan. In humans, the half-life of circulating neutrophils is about 7 hours, whereas in mice it is roughly 8-10 hours (1). Furthermore, Pillay and colleagues discovered that the mean duration of circulatory neutrophil survival is 5.4 days, as determined using in vivo labeling with 2H2O. Allegedly, the basal production rate of neutrophils is estimated to be between 5×10^{10}–10×10^{10} cells per day. This rate is necessary to provide a sufficient quantity of neutrophils in the bloodstream. Variables like as inflammation and tumors might

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boost this generation rate (2). Importantly, persistent disruption of the body's internal clock may facilitate the spread of cancer cells and the formation of secondary tumors. The diurnal rhythm of neutrophils is closely associated with the C-X-C motif chemokine receptor 2 (CXCR2) and CXCR4. The transcriptional and migratory features of circulating neutrophils are influenced by CXCR2 in a diurnal manner, leading to the ageing of neutrophils. The function of CXCR4 is to facilitate the removal of neutrophils and provide protection to the cardiovascular system (3).

Neutrophils can enter tumors and contribute to the advancement of cancers via their adaptable characteristics and functional flexibility. Tumor-associated neutrophils (TANs) exhibiting a pro-tumor phenotype participate in every phase of tumor development, including tumor initiation, metastasis, and immunosuppression (4). High levels of neutrophil infiltration in solid tumors often indicate worse clinical outcomes for patients. For example, an elevated neutrophil-to-lymphocyte ratio (NLR) in the blood is associated with a worse chance of survival in several types of solid tumors, particularly in later stages of cancer. Nevertheless, accumulating data has also shown that TANs may hinder the progression of malignancies by directly eliminating tumor cells or stimulating innate or adaptive immune responses. Thus, TANs can exhibit both pro- and anti-tumor actions inside the tumor microenvironment (TME). Furthermore, gaining a more profound comprehension of the dynamic equilibrium of TANs will aid in the advancement of treatments that specifically target neutrophils in cancer (5).

In this analysis, we examine data from published research that pertain to the transformation of neutrophils in the TME, with a specific emphasis on the impact of neutrophils in either inhibiting or facilitating tumor advancement. Additionally, this study provides a concise overview of the developing therapeutic approaches that specifically target neutrophils for the treatment of cancer (2, 8).

Source and phenotype

the source, employment, and phenotypic alterations (transitioning between antitumour and pro tumour) of neutrophils in cancer tissues have been linked to particular medical results, and current investigations have successfully identified the precise function and pathophysiology of TANs (6). Neutrophils are constantly generated and stored in the bone marrow under typical physiological conditions. The haematopoietic cords, located in the bone marrow, act as the origin of neutrophils, with typical myeloid progenitor cells being the real origin of neutrophils inside the venous sinuses. Transcription factors include CCAAT-enhancer binding protein (CEBP/α) and AML-1 (acute myeloid leukemia 1), together with colony-stimulating factors, facilitating the production of neutrophils without any problems (6).

TANs may exhibit various phenotypes because of the presence of a wide range of transcription factors and specific proteins. Several studies have classified neutrophils into distinct subsets based on various criteria to study their differentiation. In this summary, we provide the most prevalent categorization outcomes based on morphological and functional distinctions: the N1, also known as antitumour neutrophils, and the N2, also known as protumour neutrophils (7). N1 and N2 are the two cell populations that have been widely researched in terms of their physical characteristics and biological roles. Interferon type 1 (IFN-1) is primarily responsible for inducing neutrophil polarization into the N1 phenotype, which enhances adhesion, transmigration, phagocytosis, oxidative bursts, dysregulation, and the formation of neutrophil extracellular traps (NETs). Alternatively, when exposed to transforming growth factor-β (TGF-β), neutrophil differentiation advances towards the N2 state, which regulates the immune system. The transition from N1 to N2 implies that IFN-1 and TGF-β may have opposing signaling pathways. Significantly, there are clear disparities between immature N2s and mature N2s, particularly when they are subjected to certain pathological circumstances (8).

N1 cells, known as antitumour neutrophils, exhibit cytotoxicity against cancer cells by the formation of reactive oxygen species (ROS). This ROS production activates TRMP2, an H_2O_2-dependent Ca^{2+} channel, resulting in the fatal influx of calcium ions in tumor cells. Recent research has shown further methods of inhibiting cancer cells, where Ribonucleic acids (RNS) released by N1 cells are taken in by tumor cells and modify the activity of genes associated with cancer. In contrast, N2 demonstrates the capacity to promote tumor growth by producing a wide range of enzymes, including myeloperoxidase, neutrophil elastase (NE), and matrix metalloproteinases. These enzymes can modify the dense ECM to facilitate the process of angiogenesis and the migration of cancer cells (9).

The role of neutrophils in the process of tumorigenesis

Onset of cancer

In cancer start, inflammation is a vital factor since it causes tissue damage, and neutrophils play a critical part in this mechanism. Neutrophils serve as a connection between inflammation and malignancy. Ovarian cancer that arises in different mouse models with KRAS mutations demonstrates increased expression of chemokines associated with neutrophils and an expansion of neutrophil populations. The observed characteristics may be caused by the direct

increase in the production of cytokines associated with neutrophils, such as GM-CSF and CXCL8 (10). In a zebrafish model of HRASG12V-driven melanoma, the presence of wounding-induced inflammation leads to an increase in cancer growth. This increase is specifically reliant on neutrophils and is accompanied by higher levels of prostaglandin E2 (11). The use of anti-Ly6G antibodies to eliminate all neutrophils has a detrimental effect on the development of cancer in both chemically induced and spontaneous cancer models. Neutrophils that have an increased level of CXCR2 are drawn to tissues that are prone to cancer via the action of the cytokine IL-8 and chemokine ligands CXCL1, CXCL2, and CXCL5. Papilloma or adenoma development is prevented by applying chemical carcinogens to mice that are defective in CXCR2, which results in decreased neutrophil transport. The movement of neutrophils from the bone marrow to the peripheral circulation is hindered by the presence of CXCR4, which causes the neutrophils to be held back by bone marrow stromal cells that produce CXCL12. Subsequently, bone marrow macrophages remove the residual neutrophils in a rhythmic fashion (11).

Neutrophils cause DNA damage

The aforementioned research has shown the essential role of neutrophils in the development of cancer. However, further investigation is needed to fully understand the specific processes via which neutrophils promote carcinogenesis. Neutrophils generate and discharge genotoxic DNA compounds that enhance DNA instability. Using an in vitro coculture paradigm that imitates intestinal inflammation in ulcerative colitis, it has been shown that neutrophils enhance the occurrence of replication mistakes in colon epithelial cells. Activated neutrophils in persons with chronic colon inflammation lead to the buildup of target cells in the G2/M phase, which indicates the presence of a DNA damage checkpoint (12). The process may be linked to neutrophil-derived elastase, the generation of ROS and reactive nitrogen species (RNS), as well as angiogenic factors like MMP-9. Additionally, the immunosuppressive capability of neutrophils may also play a role in this process. ROS that are generated by neutrophils during chronic inflammation, such as hypochlorous acid (HOCl) produced by myeloperoxidase (MPO), induce DNA damage and exhibit carcinogenic properties in lung cells when tested in vitro. HOCl is a primary oxidizing agent produced by neutrophils. The production of HOCl by MPO during lung inflammation is a significant cause of genotoxicity generated by neutrophils. Neutrophils contribute to DNA damage by generating ROS and triggering genetic alterations in premalignant epithelial cells. This process ultimately leads to the development of oncogenic transformation in lung cancer. In addition, at normal levels seen in the body, HOCl causes mutations in the hypoxanthine phosphoribosyl transferase (HPRT) gene, resulting in three main forms of DNA damage (13). Haqqani et al. examined a mouse model of subcutaneous cancer and demonstrated a substantial correlation between the number of mutations in the Hprt locus and the levels of inducible nitric oxide synthase (iNOS) and nitric oxide synthase (NOS) as well as the infiltration of neutrophils (14). Nevertheless, a novel mechanism that is independent of ROS has been recently discovered. Excited neutrophils that infiltrate the tissues of patients with inflammatory bowel disease and injury models release particles containing pro-inflammatory microRNAs, such as miR-23a and miR-155 (15). These microRNAs contribute to the occurrence of DNA double-strand breaks and genomic instability. miR-155 is implicated in both the induction of DNA damage and the regulation of DNA repair in acute colon injury caused by neutrophils. This process has a role in the beginning and development of colorectal cancer (15).

Neutrophils stimulate the formation of new blood vessels and inhibit the immune response

Coussens et al. reported that MMP-9, produced by neutrophils generated from bone marrow and other hematopoietic cells, has a role in the development of squamous cell carcinoma. Neutrophils create MMP-9, which also plays a role in the development of pancreatic islet carcinoma and lung cancer by promoting angiogenesis. NETs contribute to inflammation in individuals with nonalcoholic steatohepatitis, leading to the formation of hepatocellular carcinoma (16). However, this process may be prevented by treating it with deoxyribonuclease or by eliminating peptidyl arginine deaminase type IV, which reduces the creation of NETs. Moreover, there is a positive correlation between NETs and the higher count of regulatory T cells (Tregs) in cancer. This correlation is achieved by aiding in the metabolic reprogramming of naïve CD4+ T cells. Therapies that focus on the interplay between these two kinds of cells or hinder the function of Treg cells may enhance the immune system's ability to detect and prevent the growth of hepatocellular carcinoma (17).

The secretion of Bv8 by neutrophils has been identified as a characteristic that indicates the development of new blood vessels in tumors, known as tumor angiogenesis. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a cell adhesion molecule that is abundantly present on Gr1+CD11b+ myeloid cells. It has the ability to inhibit angiogenesis via the G-CSF-Bv8 signaling pathway (18). Moreover, the VEGFA molecule can control almost every element of tumor angiogenesis,

such as embryonic cell sprouting and assembly, lumen development, vascular expansion, and permeabilization. Scapini et al. discovered that VEGFA generated from neutrophils plays a crucial role in the process of angiogenesis triggered by CXCL1/MIP2. TAN2 is a significant contributor of MMP9 in the TME. Neutrophil gelatinase-associated lipocalin (NGAL), generated by TAN2 and neoplastic cells, might potentially boost the pro-angiogenesis impact of MMP9. Regularly, IFN-β hinders the synthesis of VEGFA and MMP9 by neutrophils, hence inhibiting their pro-angiogenesis capability in mouse cancer models. Neutrophils have been shown to have a vital role in promoting angiogenesis at the location of a tumor (19).

Neutrophil extracellular traps (NETs)

NETs generated by TANs contribute to tumor growth via their dual functionality. The anticancer activity of NETs mostly stems from their ability to directly kill cancer cells and activate the immune system. Nevertheless, NETs are well recognized for their pro-tumor characteristics (20). In a mouse model of infection, NETs were shown to accumulate in small blood vessels and catch circulating lung cancer cells by forming DNA webs. This process ultimately resulted in the formation of small metastases in the liver. NETosis, a process that increases the quantity of circulating DNA, has the potential to cause tumor-associated stroke. Neutrophils produce MMP-9 during degranulation, which may directly hinder cell death, stimulate cell proliferation, enhance tumor angiogenesis, and facilitate the distant spread of tumor cells by breaking down the extracellular matrix (21).

NE plays a crucial role in the bactericidal activity of NETs. The expression and activity of NE are increased in many types of malignancies, such as lung carcinoma and pancreatic ductal adenocarcinoma (PDAC). There have been reports indicating that the level of serum NE is directly associated with the disease status and progression in patients with lung cancer. Additionally, it is believed that this correlation may play a role in the development and spread of primary tumors. Neutrophils-derived MMP-9 and NE were shown to be involved in the breakdown of laminin by proteolysis. This process may activate integrin α3β1 signaling, which promotes the rapid growth of latent cancer cells. The use of an antibody against MMP-9 and NE can effectively inhibit the activation of dormant cancer cells (21, 22).

The possible underlying process may include the capacity of NETs to be captured or the commencement of chemotaxis and adhesion enhanced by a DNA receptor that directly interacts with NETs or integrins. Tumor cells need an ample supply of oxygen and nutrients, which are delivered by blood vessels due to their rapid growth and development. Angiogenesis, which refers to the formation of new blood vessels, is enhanced by the release of NETs triggered by the binding of angiopoietin 1/2 to Tie 2 receptors. NETs may directly promote the growth of cancer cells. For example, Houghton et al. proposed that NETs produced in Lewis lung carcinoma might directly enhance tumor development. They observed that tumor cells grew at a slower rate in animals lacking the PAD4 enzyme compared to normal mice (21).

The relationship between the NET and tumor resistance

Drug-resistant cancer is a globally significant condition that is considered incurable, posing a serious health hazard. Research on resistance has always captivated the attention of scholars. NETs worsen the prognosis following treatment since they have been previously explained to encapsulate tumor cells and increase resistance to chemotherapy, immunotherapy, and radiation. Tumor cells secrete IL-1β under certain chemical conditions, which subsequently stimulates the generation of NETs (22). A network is established when the two essential proteins, integrin-αvβ1 and matrix metalloproteinase 9, are both present. These proteins possess the capability to capture and stimulate TGF-β. The stimulation of TGF-β triggers the onset of epithelial-mesenchymal transition (EMT) in cancer cells, which is associated with the development of resistance to chemotherapy. The resilience shown by NETs may be associated with their structural attributes. More precisely, NETs that develop inside tumor tissues operate as defensive barriers, obstructing the interaction between tumor cells and therapeutic drugs. Furthermore, the chemical composition of NETs may have a pivotal impact on resistance. For example, IL-17, an interleukin present in NETs, may engage with cytotoxic CD8 T lymphocytes and hinder their infiltration into tumor tissues (23, 24).

Tumor metastasis

Neutrophils contribute to tumor metastasis by promoting the movement, infiltration, establishment, and breakdown of the ECM by cancer cells. The upregulation of the anti-apoptotic molecule Mac-1 (CD11b, αMβ2) on the surface of neutrophils in response to lipopolysaccharide (LPS) stimulation enhances liver metastasis by facilitating the adhesion of circulating tumor cells (CTCs) (25). The secretion of IL-8 by human melanoma cells may enhance the expression of β2 integrin on neutrophils. This process is facilitated by the contact between ICAM-1 on melanoma cells and β2 integrin on neutrophils, ultimately resulting in the spread of tumor cells to other parts of the body. Leukotrienes produced by neutrophils may facilitate the migration of cancer cells to remote locations. Moreover, specifically

blocking the activity of the enzyme arachidonate 5-lipoxygenase (Alox5) that produces leukotrienes might potentially restrict the spread of cancer to other parts of the body in animal models of breast cancer (25).

Neutrophils were discovered to function as transporters and suppliers of nutrients to facilitate the spread of malignancy. Szczerba et al. revealed that neutrophils could accompany circulating tumor cells (CTCs) in the circulation, hence promoting tumor advancement and hastening the spread of cancer to other parts of the body (26). Li and colleagues discovered that neutrophils may cause the buildup of neutral lipids when stimulated by lung-resident mesenchymal cells, resulting in the spread of breast tumor cells to the lungs (27). Neutrophils have a role in controlling the spread of tumors by interacting with other immune cells and mediators. IL-1β stimulates γδ T cells to produce IL-17, which causes the growth and differentiation of G-CSF-dependent neutrophils. This, in turn, inhibits the function of anti-tumor CD8+ T cells and promotes the spread of breast cancer. Neutrophils that express CD11b and Ly6G markers can inhibit the anti-tumor activity of NK cells, hence promoting the survival of cancer cells. Furthermore, this specific kind of neutrophils has the ability to release IL-1β and matrix metalloproteinases (MMPs) to enhance the movement of cancer cells from blood vessels into surrounding tissues (28).

Focus on targeted cancer therapy

Neutrophil function alterations have a crucial role in tumor development, metastasis, and angiogenesis. Numerous clinical trials have previously been undertaken to target specific treatment locations. The combination of specific suppression of neutrophil activities and a decrease in neutrophil quantities has resulted in limited options for safe and effective treatments. These targets do not necessarily have to be exclusive to the surface of neutrophils, and the therapeutic activities might be either direct or indirect. Nevertheless, advancements are being achieved in the field of neutrophil treatment (2, 8).

Focusing on the process of metabolism

Neutrophils are the most abundant form of white blood cells found in the bloodstream. Due to their high daily production and role in systemic immunity, it is difficult to develop medicines that target all neutrophils. Such therapies also pose a risk of increasing susceptibility to other illnesses, since they impair innate immunity (29). Focusing on the unique attributes of TANs might be a viable therapeutic approach. Interestingly, focusing on glutamine metabolism seems to be a promising approach for therapy, considering that both tumor cells and TANs have a crucial need for these amino acids. A recent study used mice models with 4T1 breast tumors implanted subcutaneously. These animals were treated with JHU083, a glutaminase inhibitor. The administration of this medication led to a reduction in G-CSF levels and the movement of MDSCs, while also inducing increased apoptosis in the tumor cells (29, 30).

Focusing on NET

As previously stated, NETs may facilitate the onset and spread of tumors. Platelets that are trapped by NETosis can block the entry of circulating tumor cells into the immune system, therefore preventing metastasis (8, 28). This is especially effective in instances when the immune system is not involved and there are no opposing effects from the shear forces of blood flow. This approach signifies a recently identified therapy objective. Recent study has shown that platelet-derived factors may limit the spread of cancer cells to other parts of the body. The complement system also contributes to the therapy of tumors. C5a, a crucial element that stimulates the movement of immune cells towards inflammation and the release of inflammatory substances, may activate PMN-MDSCs to support the development and spread of cancer cells via the creation of NETs. Inhibiting C5a and its receptor C5aR1 is an effective strategy for reducing the spread of tumors (31).

Neutrophil elastase (NE) is a distinct kind of serine protease that is usually found in the main granules of neutrophils. Before modern times, research has shown that the release of NE and the creation of NETs may work together to influence the growth and spread of tumors. The NE released by neutrophils is referred to as ELANE, and it selectively eliminates various kinds of tumor cells while preserving normal cells. Nevertheless, the abundance of protease inhibitors in the TME hampers the function of NE, resulting in the safeguarding of just tumor cells. Through extensive research, we have discovered that the porcine-derived ELANE homologue is very effective in overcoming this obstacle. Unlike other ELANE homologues, it is more resistant to serine protease inhibition due to its well-preserved catalytic activity (32, 33).

Drug delivery system targeting

Neutrophils, which are the most abundant white blood cells in the circulation, play important roles in acute inflammation and immunological responses against cancer. Neutrophil recruitment, adhesion, and tissue infiltration are crucial pathological alterations in cancer. Using these chemotactic properties and replicating the genetic material into a targeted medication carrier is a potential approach to cancer treatment. There are two main types of drug delivery systems: neutrophil carriers and nanovesicles made from cellular membranes (34).

Neutrophils with chimeric antigen receptors (CAR) have been created by ingeniously modifying pluripotent stem cells by the use of CRISPR/Cas9-mediated gene integration. This method allows for the creation of several, precise anti-glioblastoma (GBM) CAR constructs. The main goal of these modified neutrophils is to effectively cross the blood-brain barrier and deliver nanodrugs that respond to the tumor microenvironment, thereby precisely targeting glioblastoma with accuracy. Utilizing R-Sio2-TPZ nanoparticles to load CAR-T cells, which have shown high efficacy in eradicating GBM cells, has been scientifically validated as a safe and effective approach in cancer treatment (35).

Extracellular vesicles (EVs), produced by cells in the body, are a naturally occurring and effective medication delivery mechanism owing to their potency and ability to kill cells (36). These particles are produced from the membrane and function in the recognition and communication between cells. Neutrophils are attracted to cancerous tissues, and there is also a high presence of extracellular vesicles generated by neutrophils in these tissues. Next, we explore strategies for increasing the production of EVs and determining suitable therapeutic medicines for loading. Simpson observed that the use of nitrogen cavitation to disturb cultured cells may significantly enhance the generation of EVs (37). In a separate investigation carried out by Coffelt et al., scientists merged nanovesicles produced from neutrophils with nanoparticles carrying carfilzomib (CFZ), a proteasome inhibitor of the second generation. This compound is referred to as NM-NP-CFZ. Previous studies have shown that NM-N0-CFZ can decrease the presence of circulating tumor cells (CTCs), which are crucial for tumor metastasis. Additionally, it also hinders the development of an early metastatic environment (38).

Conclusions

This review has emphasized the existence and importance of neutrophils in cancer and examined the clinical evidence produced from studies investigating medicines that target neutrophils to treat cancer. Neutrophils can eradicate tumor cells via either indirect or direct cytotoxic mechanisms. Furthermore, the capacity of CD8+ T cells to kill tumor cells might be improved by the adaptive immune response that is generated by neutrophils. However, neutrophils found in malignancies often exhibit both phenotypic and functional flexibility. Recent research has shown the methods via which neutrophils contribute to the advancement of tumors at several stages, including carcinogenesis, tumor development, metastasis, angiogenesis, tumor-associated thrombosis, and immunosuppression. Current clinical and preclinical research have identified numerous significant target molecules that are associated with neutrophils. These molecules have been described and their potential as both cancer diagnostic biomarkers and therapeutic targets has been highlighted.

In the future, there will be continuous progress in the field of targeted neutrophil treatment via the fast improvement of biological technology. This will lead to discoveries and developments in the study of neutrophils. A deeper understanding of the mechanics behind recently discovered treatments may be supported by conducting more complicated studies that closely mimic the intricacies of human physiology. Further research should be conducted to optimize the targeting of medications since targeted therapies are more expensive than conventional chemotherapeutic agents and there is room for improvement in their use. The integration of targeted treatment with chemotherapy seems to have more therapeutic value, given the significantly reduced occurrence of adverse effects shown in the existing clinical trials. Studies on the processes and pathways related to neutrophils might also aid in the identification of novel biomarkers that can assess the effectiveness of current treatments for patients. Collectively, these results indicate that forthcoming cancer treatments may have the potential for specifically targeting neutrophils. However, at now, therapies aimed at neutrophil targeting are not the preferred choice due to the aforementioned problems.

Authors' Contribution

Farnaz Roshan Mehr and Fatemeh Gabeleh were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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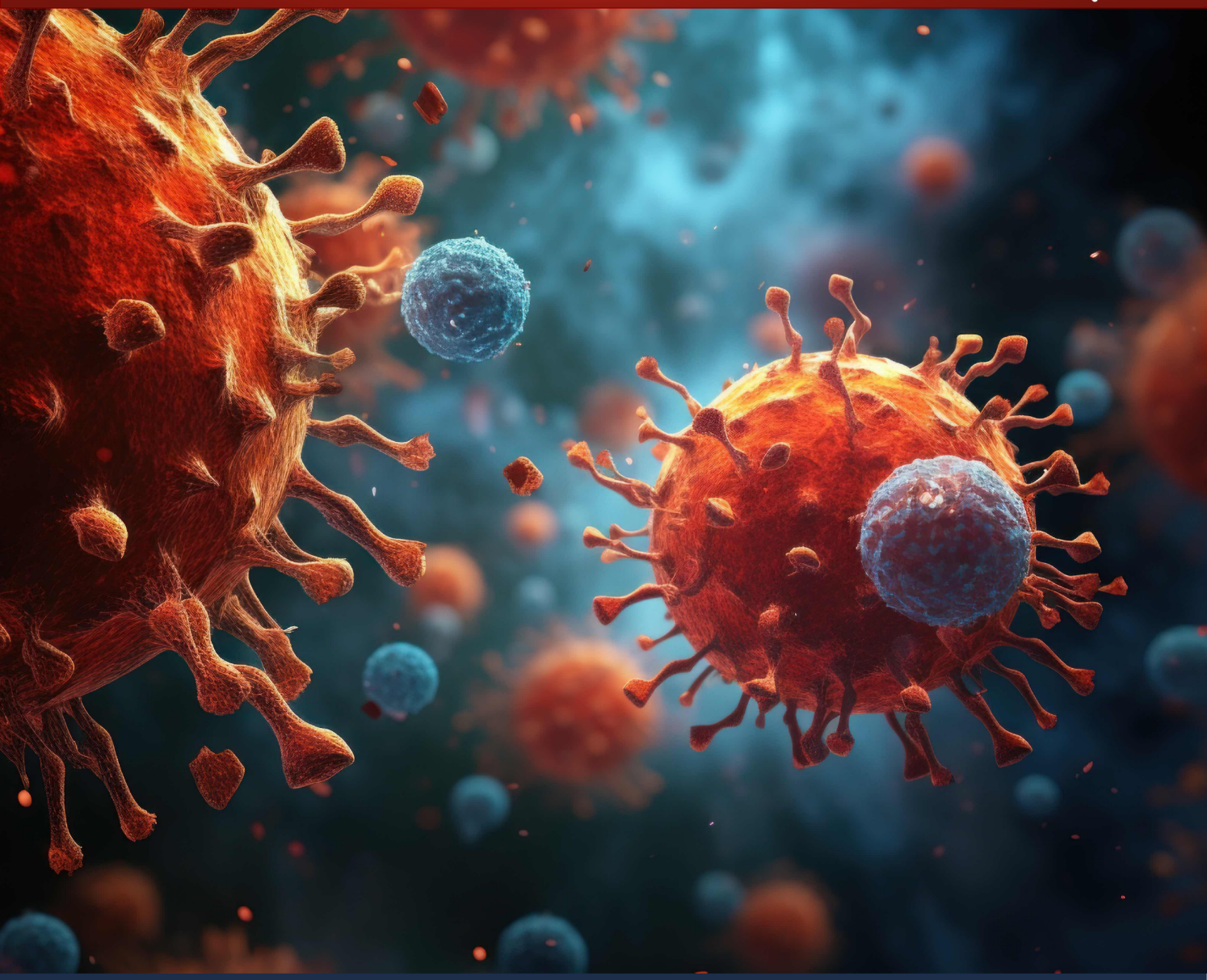

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