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Tumors and the immune system – reciprocal interaction

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Abstract
Background. Tumor formation is a multi-stage process influenced by the complex reciprocal interaction between cancer cells and the host's immune system. This relationship is described by the concept of immunoediting, consisting of elimination, equilibrium, and escape phases. Paradoxically, while the immune system can destroy cancer cells, chronic inflammation and immunosuppressive mechanisms (e.g., Treg activity, myeloid-derived suppressor cells) can promote tumorigenesis and metastasis. **Aim**. The aim of this study is to review current knowledge regarding the mechanisms of immune evasion by tumors and to evaluate the efficacy of various immunotherapy strategies, including active, passive, adoptive, and combination therapies. **Material and methods**. A comprehensive review of scientific literature was conducted using PubMed, Scopus, and Google Scholar databases. The analysis included original and review articles published primarily between 2000 and 2025, focusing on keywords such as carcinogenesis, tumor immunoediting, checkpoint inhibitors, and combination therapy. **Results**. The immune system plays a dual role in cancer development. Tumor cells employ mechanisms like MHC class I downregulation and expression of checkpoint molecules (PD-L1, CTLA-4) to evade immune surveillance. Modern immunotherapy, particularly checkpoint inhibitors (e.g., nivolumab, pembrolizumab) and adoptive cell transfer (CAR-T), has revolutionized oncology. Recent data also highlight the potential of combination therapies—pairing immunotherapy with chemotherapy, radiotherapy, or targeted therapy—to overcome resistance. Furthermore, the gut microbiota has emerged as a crucial factor modulating the response to immunotherapy. **Conclusions**. Immunotherapy represents a pillar of modern oncology. However, the heterogeneity of tumor microenvironments necessitates personalized approaches.
Keywords: carcinogenesis, tumor immunoediting, immunotherapy, combination therapy

1. Introduction

Carcinogenesis is a multi-stage process. Physical, chemical, and biological carcinogenic factors affect the organism directly or indirectly, inducing the formation of endogenous intermediate factors, most often reactive oxygen species and their derivatives. They cause DNA damage and the formation of mutations, which can lead to neoplastic transformation of the cell if they concern stem cells and are not repaired. The reciprocal interactions between the immune system and the tumor are captured by the concept of tumor immunoediting. Stage I is the elimination of tumor cells and inhibition of tumor growth. In stage II, an equilibrium is established between elimination and the formation of new tumor cells, until finally, in stage III, the so-called "escape", tumor cells escape immune surveillance, are recognized as self, and thus are not removed. This means that immune system cells can fight tumor cells, but paradoxically also influence their initiation, promotion, and metastasis. [1] The presence of leukocytes in tumor sections was considered a normal immune system response to cancer-transformed cells. The role of the immune system in the process of carcinogenesis is indispensable, however, inflammation within the tumor is a completely different type of inflammation. Most solid tumors induce an internal immune response that builds the microenvironment. Tumor cells secrete factors from the RAS or MYC group, which cause tissue remodeling, increasing lymphocyte and leukocyte infiltration, whereby in every solid tumor, nutrient and oxygen deficiencies occur due to the rapid growth of tumor mass. This results in the death of many tumor cells and the release of pro-inflammatory factors from them. Leukocytes are therefore

actively recruited to the tumor microenvironment as a reaction to these factors, and then reprogrammed by the tumor to its advantage. [2]
Studies of tumor antigens can serve for their detection, monitoring of development, and therapy, e.g., using monoclonal antibodies or vaccines. Since many tumor antigens are not specific and occur on normal cells, they are called tumor-associated antigens (TAA). Exceptions are specific tumor antigens, which are immunogenic. Tumor cells often possess the CD47 molecule inhibiting phagocytosis; blockade of these molecules is attempted in cancer immunotherapy. [3]
The classic division of immunotherapy includes 3 forms: active, passive, and adoptive. In active immunotherapy, modified tumor cells, their antigens, or stimulating preparations are administered to increase the patient's immunological reactivity. Passive immunotherapy involves the use of specific monoclonal antibodies and non-specifically acting anticancer cytokines, i.e., TNF-alpha. Adoptive immunotherapy involves the administration of previously activated immune system cells intravenously or locally. [4]

2. Material and methods

This paper constitutes a narrative review of the scientific literature concerning the biological mechanisms of the immune response to cancer and clinical applications of immunotherapy. A comprehensive search of medical databases, including PubMed, Scopus, and Google Scholar, was conducted. The search strategy utilized the following keywords and their combinations: "carcinogenesis", "tumor immunoediting", "immunotherapy", "immune checkpoint inhibitors", "CAR-T cells", and "combination therapy".
The analysis included original research articles, clinical trials, and review papers published primarily between 2000 and 2025. Particular emphasis was placed on recent studies (2020–2025) describing novel therapeutic agents (e.g., LAG-3 inhibitors, BiTEs) and the role of the gut microbiota in immune modulation. Articles were selected based on their relevance to the reciprocal interaction between tumor cells and the immune system, as well as the efficacy of therapeutic interventions. The collected data were synthesized to present the dual role of the immune system in tumorigenesis and the current state of immuno-oncology.

3. Results

3.1. The role of the immune system in the pathogenesis of tumors

Basics of the immune reaction Upon contact with an antigen, the organism initiates an immune response consisting of an induction phase and an effector phase. It can be divided according to various categories, including: mechanism (humoral and cellular response), specificity (specific and non-specific response), speed and duration of reaction (primary and secondary response). The most important cell types participating in the immune reaction include B lymphocytes, T lymphocytes, phagocytes, and antigen-presenting cells. Furthermore, essential molecules include antigen-binding receptors (on T cells) and immunoglobulins (produced by B lymphocytes). The induction phase is characterized by the binding of lymphocytes to antigens. Thus bound, they proliferate and begin to differentiate into effector cells. In the second stage, the effector phase, effector cells participate in the response against the antigen.
In the humoral type response, the antigen is recognized by B lymphocytes, as well as by antigen-presenting cells. After cooperation with T lymphocytes, B lymphocytes are activated, followed by their intense proliferation and differentiation. The final form of cells into which B cells differentiate are plasma cells, producing antibodies. Antibodies bind to antigens, inducing various reactions, among others: complement activation, induction of immunophagocytosis, toxin binding, agglutination. In the case of cellular response, the main cells participating in the

reaction are T lymphocytes. Following binding with antigens, they produce cytokines, inducing diverse reactions, such as induction of inflammation, stimulation of phagocytes, immunosuppression.

Table 1. Selected cells of the immune system and their example functions.

Cell	Functions
B Lymphocytes	Recognition of antigens. Production of antibodies (key element of humoral response). Presentation of antigens to T lymphocytes.
T Lymphocytes	Secretion of cytokines (Th, Treg) Supporting immune response (Th) Inhibiting excessive immune reaction (Treg) Killing target cells (Tc)
Dendritic cells (DC)	Antigen-presenting cells Cytokine secretion
NK Cells	Can spontaneously kill tumor cells and virus-infected cells
Monocytes/macrophages	Phagocytosis Cytokine production
Neutrophils	Phagocytosis Secretion of antimicrobial substances via degranulation Release of neutrophil extracellular traps (NETs)

Table 1. Selected cells of the immune system and their example functions.

The immune system and tumorigenesis

The immune system plays a complex role in tumor development and progression. Immune system diseases obviously contribute to increased susceptibility to infections and tumor development. This is the case, for instance, in AIDS (Acquired Immunodeficiency Syndrome) or during the use of immunosuppressive drugs after transplantation. When the immune system undergoes increased activation, it can also contribute stimulatively to tumorigenesis. In inflammatory bowel diseases, a significantly elevated level of Th17 lymphocytes has been demonstrated, which is associated with an increase in the incidence of colorectal cancer. It is widely believed that immune system cells, such as cytotoxic NK cells or CD8+ T lymphocytes, by eliminating more immunogenic tumor cells, influence the selection of less immunogenic cells, and thus less detectable by the immune system. Immune cells and cytokines can also contribute to inducing immunosuppression, proliferation of tumor cells, and metastasis formation [5].

In this subsection, the role of cellular and molecular components of the immune system in the pathogenesis of tumors will be discussed. Macrophages are divided into type M1 – pro-inflammatory, attracted by lipopolysaccharides (LPS) and IFN-γ, and type M2 – anti-inflammatory, attracted by IL-4 and IL-13. Depending on the participation of a specific macrophage type, the effect exerted by them is different [6]. M1 macrophages eliminate tumor cells that have a more immunogenic character. As the tumor progresses, the number and function of M1 macrophages decrease, and M2 macrophages gain advantage, which are called TAM – tumor-associated macrophages [7]. TAM cells can constitute up to 50% of the tumor mass [8]. Depending on the released factors, TAM exert various effects through which tumor development proceeds. Release of IL-10 and TGF-β causes immunosuppression (weakening of T lymphocytes and inhibition of dendritic cell maturation) [9,10,11]. Secretion of vascular endothelial growth factor (VEGF) stimulates angiogenesis [12], matrix metalloproteinases (MMP) [13] facilitate remodeling of the extracellular matrix, and epidermal growth factor (EGF) promotes proliferation of tumor cells [14]. The predominance of M1 or M2 macrophages is associated with tumor prognosis – it has been shown that a higher number of M1 macrophages in lung cancer influences a better prognosis [15].

Neutrophils are the first to reach the altered tissue. Neutrophils associated with the tumor are called TAN – tumor-associated neutrophils. Similarly to macrophages, they can occur in two forms – N1 (protumor) and N2 (antitumor) [16]. Migration of neutrophils to the neoplasm-altered site takes place thanks to chemokines CXCL1, CXCL2, CXCL5, which are secreted, e.g., by tumor cells [17]. Elastase contained in neutrophils, after release under inflammatory conditions, affects the development of angiogenesis, stimulation of tumor cell proliferation, and their invasion [18]. Also important is the role of NETs, i.e., neutrophil extracellular traps, consisting mainly of chromatin, proteases, and intracellular proteins. Their function in tumor development is associated with metastasis formation. Traps thrown by neutrophils trap tumor cells in one place, thereby increasing their concentration in the same location [19].

NK cells detect tumor cells that do not possess MHC I receptors on their surface [20]. Thanks to this, their presence at the tumor site is associated with a better prognosis, as for example in colorectal cancer [21]. Elimination of tumor cells by NK cells takes place thanks to perforins and granzymes secreted by them, thanks to the release of TNF-α and direct activation of TRAIL and FasL pathways [22]. In a study conducted on mice, it was proven that along with abnormal proliferation and activation of the RAS pathway, ligands recognized by NKG2D receptors on NK cells are produced in tumor cells. In mice that did not show the presence of the NKG2D receptor on NK cells, the likelihood of tumor development was greater [23].

Following the macrophage pool, the second largest population of immune system cells in a tumor are T lymphocytes. Among them, CTLs dominate, i.e., cytotoxic T lymphocytes, differentiating from CD8+ T lymphocytes. They migrate directly to the tumor under the influence of chemotactic and adhesive factors. By releasing granzymes and perforins via exocytosis, they exert an antitumor effect – causing the death of tumor cells [24]. However, there are defense mechanisms of attacked cells, which via FasL on their surface, induce lymphocyte apoptosis [25]. It was observed that in patients with lung cancer, the population of lymphocytes expressing the Fas receptor on their surface is larger compared to healthy individuals; a similar dependence occurs respectively in smokers and non-smokers [26]. Additionally, Th1 CD4+ lymphocytes are present in tumors, which by secreting large amounts of cytokines IL-2, TNF-α, IFN-γ, stimulate CTL activation, as well as the antitumor action of macrophages and NK cells [27].

Another way to weaken the immune response is the lack or smaller amount of costimulatory molecules on the surface of tumor cells and antigen-presenting cells. In an undisturbed mechanism, the costimulatory signal is transmitted by CD80 and CD86 molecules located on APCs to the CD28 receptor on the surface of lymphocytes. After signal transmission, full activation of lymphocytes occurs. There is also a way of suppressing the transmission of the activation signal through the interaction of CD80 and CD86 with the CTLA-4 receptor. Such a connection blocks signal transmission through the TCR receptor. CTLA-4 is a compound homologous to CD28, however, it binds to CD80 and CD86 about 40 times more strongly [28]. The CTLA-4 molecule can be found on Treg lymphocytes. Treg lymphocytes have the ability to suppress the immune response by inhibiting dendritic cells, CD4+ CD8+ T lymphocytes, and NK cells. An important role in activating the suppressor function of Treg is played by the Foxp3 molecule on their surface. It has been shown that Foxp3 and CTLA-4 expression on the surface of Treg is associated with a worse prognosis, e.g., in lung cancer [29].

In the case of B lymphocytes, their role in the development and progression of tumors was not yet investigated as thoroughly as in the case of T lymphocytes until recently. It was believed that due to their secretion of IL-10 and TGF-β [30, 31], they may exert immunosuppression in the tumor environment. New reports from 2024–2025 revise the view on the role of B lymphocytes. Their presence in the tumor, especially when forming organized clusters called tertiary lymphoid structures (TLS), is associated with a better response to immunotherapy and longer patient survival (including in melanoma and gastric cancer). Mature TLS act as local immunity training centers where B lymphocytes present antigens to T lymphocytes and produce antitumor antibodies [32], [33]. Besides, by activating myeloid cells via FcRγ, they can indirectly stimulate angiogenesis and chronic inflammation [34]. The role played by the immune system in the pathogenesis of tumors is complicated, and deeper understanding of its mechanisms and explanation of exactly how transformation occurs will allow the development of more precise and effective therapeutic methods [35,36].

Immunoediting

In the tumor microenvironment, immunoediting takes place – a process involving the reprogramming of immune system cells by the tumor so that they act to its advantage. It is divided into three phases: elimination, equilibrium, and escape. In the elimination phase, tumor cells present their own antigens via MHC I molecules. This leads to the induction of an immune response that can eliminate tumor cells, however, if this does not happen, the equilibrium phase follows. At this stage of immunoediting, the processes of immune cell proliferation and their removal by immune cells equalize. It is assumed that the escape phase is a consequence of

mutations and changes occurring in tumor cells. Studies have shown the following changes: loss of HLA class I proteins; loss of LMP2 and LMP7 subunits of immunoproteasomes; lack or impaired function of the receptor for IFN-γ, which causes a lack of response to this molecule. The escape phase is also influenced by the overproduction of immunosuppressive cytokines, such as IL-10 and TGF-β. Overproduction of T-cell response inhibitors has also been demonstrated: galectin-1, indoleamine 2,3-dioxygenase. In developing tumors, suppression of pro-inflammatory signal induction was also detected, which may lead to impaired maturation of dendritic cells. Thus, there are many mechanisms that enable tumor cells to avoid the immune response. Such escape from immune control leads to unlimited tumor growth [37].

However, the most important mechanism of tumor escape from immune surveillance turned out to be the ability of tumor cells to express on their surface molecules inducing T lymphocyte anergy. CTLs remain active if, after antigen recognition, they receive a stimulating signal derived from the connection of costimulatory molecules on the lymphocyte and APC cells or tumor cells. The most important connection is the bond between the CD28 molecule on lymphocytes and B7.1 (CD80) or B7.2 molecules on APC or tumor cells. However, CD28 can be displaced by the CTLA-4 molecule (cytotoxic T-lymphocyte-associated antigen 4), which is also found on the surface of T lymphocytes. Then the lymphocyte, even though it recognized the antigen presented by APC, remains inactive. Lymphocytes can also undergo apoptosis or remain in a state of anergy as a result of the connection of the PD-1 molecule (programmed cell death) occurring on their surface with PD-L1 or PD-L2 ligands found on tumor cells and antigen-presenting cells. Such a connection is sometimes referred to as the formation of a "negative immunological synapse". Such inhibitory immune response checkpoints on lymphocytes also include molecules: BTLA (B and T lymphocyte attenuator), VISTA (V-domain Ig suppressor of T cell activation), TIM-3 (T cell immunoglobulin and mucin domain 3), and LAG3 (lymphocyte activation gene 3). Contemporary and most effective immunotherapy methods involve blocking the formation of the "negative immunological synapse" in lymph nodes and in the tumor and involve the use of checkpoint inhibitors.

Therapeutic modifications of the immune response Immunotherapy relies largely on stimulating specific components of the immune system to enhance the antitumor response. The classic division of immunotherapy includes 3 forms: active, passive, and adoptive.

Active non-specific immunotherapy In active immunotherapy, modified tumor cells, their antigens, or stimulating preparations are administered to increase the patient's immunological reactivity. In 1893, William Coley noticed the disappearance of sarcoma in a patient who was simultaneously suffering from a bacterial infection. So he began using so-called Coley's toxins in cancer therapy, which contained microbes causing erysipelas. The infection activated an immune response, which in some cases also acted on tumor cells and caused tumor regression. This type of immunotherapy, i.e., active non-specific immunotherapy, involves stimulation of all components of the immune system, i.e., APC cells, T and B lymphocytes, production of pro-inflammatory cytokines and antibodies by bacterial antigens. The reaction was directed against bacterial antigens, however, it enabled more efficient uptake and presentation of tumor antigens, as well as stronger activation of lymphocytes and triggering of non-specific antitumor response (activity of macrophages and NK cells). In the 90s, the use of pro-inflammatory cytokine preparations directly stimulating the immune system began, mainly interleukins and substances enhancing their production. In 1969, lon Gresser and colleagues discovered the anticancer effect of interferon. Increased survival of mice suffering from cancer administered interferon was noted [38]. Currently, it is known that the basis of the anticancer action of interferons is the inhibition of oncogenic virus replication and modulation of differentiation and development

processes of immune system cells, mainly macrophage activation by IFN-γ [39]. Coley's toxins were used until the 1960s. Another example of active non-specific immunotherapy is the use of the BCG vaccine preparation registered in the 90s in intravesical instillation in patients with bladder cancer [40]. In the 90s, the use of pro-inflammatory cytokine preparations directly stimulating the immune system began, e.g., IL-2 in patients with advanced melanoma and renal cancer, lenalidomide increasing IL-2 production in patients with multiple myeloma, immunostimulant levamisole in patients with advanced colorectal cancer, and interferon alpha-2b in postoperative treatment of patients with melanoma. Such treatment was, however, burdened with high toxicity and not very effective [41, 42].

Active antigen-dependent immunotherapy Immunotherapy using tumor cell antigens or whole tumor cells is based on the concept of antigenic difference between tumor cells and normal body cells. The immunogenicity (ability to induce an immune response) of a tumor is greater the more mutations occurred in exons in the tumor cell DNA and the more antigens different from autologous ones were formed as a result. Such tumors include, e.g., melanoma, squamous cell lung or head and neck cancers, and those resulting from viral infection. Qualification for this type of immunotherapy requires demonstration of MHC class I molecule expression [43].

Antigen-independent immunotherapy targeting immune checkpoints In the vicinity of the tumor, regulatory T lymphocytes, suppressor cytokines, myeloid-derived suppressor cells, and protein costimulatory molecules with suppressive activity - immune system checkpoints - occur in large quantities [45]. For T lymphocyte activation to occur, it must receive costimulatory signals from PD-1 and CTLA-4 molecules, otherwise it will enter a state of anergy (inability to react to an antigen). Anergy will also occur when receptors - immune system checkpoints - are activated [46]. Costimulatory molecules in healthy tissues prevent autoimmunity, however, in the tumor environment, they may be responsible for the "escape" mechanism from immune surveillance. Contemporary and most effective immunotherapy methods involve blocking the formation of the "negative immunological synapse" in lymph nodes and in the tumor [47]. Inhibition of this negative immune regulation was the subject of work for which James P. Allison and Tasuku Honjo received the Nobel Prize in 2018. Blockade of CTLA-4, PD-1, and PD-L1 enhances the antitumor immune response by increasing the infiltration of effector T lymphocytes into the tumor microenvironment and inhibiting the migration of Treg lymphocytes into this environment [48]. Thanks to these observations, the drugs Ipilimumab and tremelimumab were developed, which were approved as anti-CTLA-4 monoclonal antibodies. In patients, the anti-PD-1 monoclonal antibody named MDX-1106 (later nivolumab) is well tolerated and shows antitumor activity [49]. Another anti-PD-1 antibody used in immunotherapy is pembrolizumab. Less frequently used include, among others, pidilizumab [50]. Thanks to these antibodies, success has been achieved in the therapy of various cancers, including melanoma, lung, kidney, bladder cancer, and Hodgkin lymphoma [51].

In 2022, relatlimab – the first antibody blocking the LAG-3 checkpoint – was introduced into clinical practice. In combination with nivolumab (anti-PD-1), this drug showed higher efficacy in extending progression-free survival in patients with advanced melanoma compared to anti-PD-1 monotherapy [52], [53]. In recent years (2023–2024), the key role of gut microbiota in modulating the response to checkpoint inhibitors (ICI) has been proven. The composition of gut bacteria (e.g., presence of Akkermansia muciniphila) influences systemic immunity by producing metabolites such as short-chain fatty acids (SCFA), which strengthen T lymphocyte function and seal the intestinal barrier. Gut dysbiosis is currently recognized as one of the factors of resistance to immunotherapy [55].

Passive non-specific immunotherapy It involves the administration of non-specifically acting antitumor cytokines, which are the basic executive and communication tool of the components of the entire immune system. Many antitumor effects of cytokines have been recognized: direct cytotoxic effect (TNF-α), modification of lymphocyte migration (TNF, IL-1, INF-γ); increasing the sensitivity of tumor cells to cytotoxic effects of various biological or chemical factors (INF-γ, TNF-α); inhibition of tumor cell proliferation (INF-α, INF-γ), and activation of NK cells (GM-CSF, IL-2, IL-6).

Table 2. Registered recombinant cytokine preparations.

Cytokine	Use in treatment
INF- α	- Hairy cell leukemia - T-cell lymphoma of the skin - Chronic myeloid leukemia - Disseminated renal cancer - Carcinoid - Multiple myeloma - Kaposi's sarcoma
IL-2	- Palliative treatment of renal cancer (USA)

Table 2. Registered recombinant cytokine preparations. Źródło: Source: Mackiewicz J, Mackiewicz A. Cancer immunotherapy and perspectives of its development. Contemp Oncol (Pozn). 2010;14:2.

3.2. Passive specific immunotherapy

It involves the use of specific monoclonal antibodies directed at tumor cell antigens or specially modified lymphocytes – this type of therapy is called adoptive. Linking a specific antibody with a cytostatic drug, radioisotope, enzyme, or toxin can directly lead to the death of the tumor cell that will be coated with it. The list of FDA-approved antibodies in cancer immunotherapy is presented in Table 3. The therapy uses tumor-infiltrating lymphocytes, which are collected from the patient, multiplied in the presence of IL-2 and activated, and then transfused back to the patient [56].

Table 3. FDA-approved monoclonal antibody preparations.

Monoclonal antibody	Isotype	Target	Indication
Rituximab	Chimeric IgG1	CD20	CD20(+) non-Hodgkin follicular lymphomas; diffuse large B-cell non-Hodgkin lymphomas; chronic lymphocytic leukemia
90Y ibritumomab tiuxetan	Murine IgG labeled with isotope	CD20	CD20(+) non-Hodgkin follicular lymphomas
131I tositumomab			
Alemtuzumab	Humanized IgG1	CD53	Chronic lymphocytic leukemia
Gemtuzumab ozogamicin	Recombinant humanized IgG4 – linked to calicheamicin	CD33	Acute myeloid leukemia
Trastuzumab	Humanized IgG1	HER2/neu	HER2(+) breast cancer; gastric cancer
Cetuximab	Chimeric IgG1	EGFR	EGFR(+) colorectal cancer; squamous cell carcinoma of the head and neck
Panitumumab	Human IgG2	EGFR	EGFR(+) colorectal cancer
Bevacizumab	Humanized IgG1	VEGF	Colorectal cancer; breast cancer; non-small cell lung cancer; renal cancer

Table 3. FDA-approved monoclonal antibody preparations. Źródło: Source: Mackiewicz J, Mackiewicz A. Cancer immunotherapy and perspectives of its development. Contemp Oncol (Pozn). 2010;14:2.

3.3. Immunotherapy using bispecific antibodies (BiTEs)

This therapy enables the creation of a connection between a cytotoxic T lymphocyte and a tumor cell, without prior antigen presentation via MHC molecule. BiTEs possess such properties thanks to their specific structure, enabling recognition and binding of both the lymphocyte CD3 molecule and the tumor antigen. In the USA, a BiTE antibody named blinatumomab (specific to CD19 molecule) has been registered for the treatment of patients with B-cell acute lymphoblastic leukemia without BCR-ABL rearrangement [57].

3.4. Immunotherapy through the use of CAR-T lymphocytes

Adoptive immunotherapy involves the administration of previously activated immune system cells intravenously or locally [58]. A discovery of recent years are genetically modified ex vivo T lymphocytes expressing a chimeric antigen receptor (CAR). This receptor consists of an antigen-binding domain linked to the CD3 molecule of the T-cell receptor. Thanks to this, CAR-T lymphocytes can recognize antigens and kill tumor cells without prior recognition of antigens presented by MHC. CARs can also contain an intracellular domain of costimulatory molecules, such as CD28 or 4-1BB.

3.5. Immunotherapy in combination with other treatment methods

Immunotherapy currently constitutes a popular method of cancer treatment; it has revolutionized the therapeutic process, especially in people whose disease was considered incurable. However, resistance to single-agent immunotherapy often occurs, which determines treatment failure. Hence, combining immunotherapy with other cancer treatment methods is noteworthy. In this chapter, an overview of the current state of combination therapies (combining immunotherapy with chemotherapy, radiotherapy, and targeted therapy), rationale for their use, and combination therapies approved by the US Food and Drug Administration will be discussed.

3.5. Combination of chemotherapy and immunotherapy

Interdependence between these methods has been demonstrated in mouse models. In mice, the tumor response to anthracyclines was significantly improved, while simultaneously not damaging the immune system [61]. Many studies have demonstrated the participation of cytotoxic chemotherapy in antitumor immunity, which influenced the approval by the FDA of several combination therapies with immunotherapy [62]. The mechanisms of therapy action are extremely complex. The main benefit of using cytotoxic chemotherapy is the reduction of tumor mass. Tumor cells are the main factor contributing to the alteration of the tumor microenvironment. Reducing the mass of tumor cells also reduces the production of immunosuppressive factors. Additionally, it reduces the number of cancer cells that must be eliminated by immune cells. Another mechanism is immunogenic cell death (ICD). It is a form of regulated cell death that exhibits susceptibility to activating adaptive immune response in immunocompetent hosts [63]. Numerous studies have shown that cytotoxic chemotherapy induces this process and enhances immunotherapy [64]. It may prove significant to use ICB in combination with ICD, which not only directly kill tumor cells but also increase tumor immunogenicity and induce antitumor immune responses. Nanoparticles may possess the ability to modulate systemic biodistribution and achieve targeted accumulation of administered therapeutic agents, thus facilitating clinical translation of immunotherapies based on ICD inducers in a safe and effective manner [65].

Small cell lung cancer is characterized by a particularly poor prognosis (median survival time is approx. 8 months) and occurs with a frequency of 15% of lung cancers. The gold standard of its therapy in the generalized stage is chemotherapy with platinum-based compounds and subsequent prophylactic irradiation of the central nervous system if disease progression has not occurred. Combining immunotherapy with chemotherapy can make treatment more effective and more pleasant for patients. This was shown by the results of the IMpower133 study. The possibility of treatment with atezolizumab (PD-L1 inhibitor) for patients with SCLC is one of the highest priorities for the current years to achieve better treatment results. They will not be as spectacular as in the case of non-small cell lung cancer, but certainly, such treatment will increase the comfort of life of patients [69]. Significant progress in small cell lung cancer (SCLC) immunotherapy is the FDA approval (November 2025) of the drug tarlatamab. It is a bispecific T-cell engager (BiTE) antibody that binds simultaneously to the DLL3 antigen on the

surface of tumor cells and the CD3 receptor on T lymphocytes. This mechanism allows for direct targeting of cytotoxic T lymphocytes against tumor cells, independent of antigen presentation by MHC, which significantly extends patient survival after chemotherapy failure [70], [71].

Table 4. FDA-approved chemoimmunotherapy combinations.

Nowotwór	Linia terapii	Chemioterapia	Immunoterapia
NSCLC-non-squamous	przerzut, pierwszego rzutu	pemetreksed + platyna	Pembrolizumab
NSCLC-non-squamous	przerzut, pierwszego rzutu	karboplatyna + nab-paklitaksel	Atezolizumab
NSCLC-non-squamous	przerzut, pierwszego rzutu	karboplatyna + paklitaksel + bewacyzumab	Atezolizumab
NSCLC	przerzut, pierwszego rzutu	platyna	Niwolumab + ipilimumab
NSCLC - squamous	przerzut, pierwszego rzutu	karboplatyna + paklitaksel/ nab-paklitaksel	Pembrolizumab
SCLC	stan zaawansowany, pierwsza linia	karboplatyna + etopoztd	Atezolizumab
SCLC	stan zaawansowany, pierwsza linia	karboplatyna + etopozyd	Durvalumab
Nowotwór piersi potrójnie negatywny	przerzut, pierwszego rzutu	nab-paklitaksel	Atezolizumab
Nowotwór piersi potrójnie negatywny	przerzut, pierwszego rzutu	nab-paklitaksel/ paklitaksel/ karboplatyna + gemcytabina	Pembrolizumab
Nowotwór pęcherza moczowego	przerzut, pierwszego rzutu, podtrzymywanie remisji	Gemcytabina + cisplatyna/karboplatyna	Awelumab
Nowotwór głowy i szyi	przerzut, pierwszego rzutu	platyna + 5-FU/platyna + 5-FU + cetuksymab	Pembrolizumab

Table 4. FDA-approved chemoimmunotherapy combinations. Źródło: Source: Zhu S, Zhang T, Zheng L, et al. Combination strategies to maximize the benefits of cancer immunotherapy. J Hematol Oncol. 2021;14:156.

3.7. Combination of radiotherapy with immunotherapy

Stimulation of antitumor immunity by radiotherapy was first suggested in case reports with regression of distant untreated tumors after application of local RT [72]. It is a rare and elusive phenomenon, but nevertheless aroused immense interest with the emergence of immune checkpoint blockade. The first report presenting benefits from radiotherapy and immunotherapy came from a patient with melanoma, in whom disease progression was observed during a clinical trial using ipilimumab, but tumor reduction occurred after radiotherapy [73]. Radiation causes strengthening of antitumor immunity. Radiotherapy can enhance both antigenicity and adjuvanticity. Tumor antigenicity is enhanced in many pathways. Similarly to chemotherapy, irradiation can induce MHC-I expression and enhance tumor antigen presentation [74]. Furthermore, radiation induces ICD and reduces CD47 expression on the cell surface, enhances uptake by tumor cells and antigen presentation [75]. Additionally, as a result of radiation, reactive oxygen species (ROS) are generated, which can modify macromolecules (DNA, proteins), and thus increase antigenicity, and are also crucial for tissue damage [76].

3.8. Combination of targeted therapy with immunotherapy

Tumors are associated with genomic changes that drive oncogenesis. Targeting these changes can have a direct antitumor effect [83]. There are several potential mechanisms. The first is direct antitumor activity and inducing immunogenic cell death. Elimination of tumor cells can not only reduce the number of these cells but also eliminate immunosuppressive factors and increase immunotherapy efficacy. An important factor to consider is immunogenic cell death induced by targeted therapy. There is an enhancement of tumor cell uptake and antigen presentation, stimulation and activation of the immune response, attraction of immune cells to tumor sites, and strengthening of antitumor immunity. There is also a direct effect on immune cells. The VEGF-VEGFR pathway plays a key role in almost every immune cell subpopulation [84]. Elevated VEGF levels in plasma are associated with an increased number of immature dendritic cells, and surgical removal of tumors partially reverses these effects [85].

Table 5. FDA-approved targeted therapy and immunotherapy combinations.

Tumor	Therapy line	Targeted therapy	Immunotherapy
Kidney cancer	metastasis, first line	Axitinib	Pembrolizumab
Kidney cancer	metastasis, first line	Cabozantinib	Nivolumab
Kidney cancer	metastasis, first line	Axitinib	Avelumab
Endometrial cancer not MSI-H or dMMR	metastasis	Lenvatinib	Pembrolizumab
Hepatocellular carcinoma	unresectable, first line	Bevacizumab	Atezolizumab
BRAF V600(+) advanced melanoma	advanced, first line	Vemurafenib + cobimetinib	Atezolizumab

Table 5. FDA-approved targeted therapy and immunotherapy combinations. Źródło: Source: Zhu S, Zhang T, Zheng L, et al. Combination strategies to maximize the benefits of cancer immunotherapy. J Hematol Oncol. 2021;14:156.

4. Summary and Conclusions

In this review, the role of the immune system in the pathogenesis of tumors was discussed, detailing specific cells of this system and cytokines. The literature review also concerned the current state of knowledge on various types of immunotherapy and their efficacy. The rationale for combining immunotherapy with other treatment methods seems significantly promising. This strategy allows, on the one hand, for direct killing of tumor cells, and on the other, for lifting the inhibition of exhausted lymphocytes increasing checkpoint expression. Combination therapy is unfortunately demanding in terms of clinical trials, however, new preparations and new combinations of existing drugs can give hope for a breakthrough in immuno-oncology.

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