REVIEW

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New Developments in Oncological Treatment: Targeted Treatments and Immunotherapy

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Abstract

In the last 20 years, when we started to understand cancer biology better, targeted therapies and immunotherapies have been developed in systemic treatments and they have started to take their place as monotherapy or combined therapies in routine practice. Treatments that affect specific molecules are called targeted therapies. Monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKIs) and those affecting the proliferation cascade constitute the majority of targeted therapies currently used. mAbs are targeted molecules produced from a single B-cell clone by antigen exposure. Most immunotherapeutics currently in use are in the form of mAbs. The targets of mAbs that we frequently use in cancer treatment today are human epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor, nuclear factor kappa-B ligand receptor activator, programmed death-1 and programmed death ligand-1. Treatments for tyrosine kinases, which play an important role in growth signal modulation, are used in many types of cancer. TKIs are small molecules and are used orally. The most commonly used TKIs are anti-angiogenic multikinase inhibitors. However by the EGFR and anaplastic lymphoma kinase inhibitors, a great progress has been made especially in the treatment of non-small cell lung cancer. Again BRAF/MEK, smoothened/hedgehog pathway, poly (ADP-ribose) polymerase, phosphoinositide 3-kinase, HER-2 inhibitors are other TKIs in use. The mammalian target of rapamycin pathway is also used as a target in many cancers. Immunotherapies are therapies that regulate the immune microenvironment, strengthening the immune system and allowing immune cells to fight against tumor cells. The effect of immunotherapy on cancer cells has been demonstrated by the high dose interferon, which was the first immunotherapy used. It consists of cancer vaccine, oncolytic viruses, *ex vivo* activated T-cell and natural killer cell transfer and immune checkpoint inhibitors. All these treatments contribute significantly to the survival and quality of life of patients with more antitumor efficacy. A large number of new molecules are being researched going forward, and promising advances in cancer treatment will continue.

Keywords: Cancer, targeted therapy, immunotherapy

INTRODUCTION

Traditional cancer treatment consists of surgery, radiotherapy and chemotherapy. While surgery and radiotherapy are mostly used in localized disease, systemic chemotherapy is mostly used as the primary treatment in metastatic disease. However, since conventional chemotherapeutic drugs mostly target rapidly growing cancer cells, they also cause many undesirable side effects by affecting fast growing normal tissues such as blood and gastrointestinal system cells. In the last two decades, targeted therapies that eliminate or inactivate cancer cells have been developed with a better understanding of cell chemistry and genome (1,2). Treatments that aim for a specific molecule and aim for more effect and less side effects are called targeted therapies. In this article, we tried to talk about target therapies and immunotherapies that have broken ground in oncology in recent years.

Targeted agents in oncology can be classified as: Monoclonal antibodies (mAbs), tyrosine kinase inhibitors (TKI), those affecting

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the proliferation cascade, and others. In Table 1, we tried to summarize some of the targeted drugs and immunotherapy options detailed in this article and that can be used in most of our country.

TARGETED TREATMENTS

1- Monoclonal Antibodies

Antibodies are molecules formed by antigen exposure by B lymphocytes. Antibodies produced by the normal immune system are polyclonal and are produced from many B lymphocyte clones. On the other hand, mAbs used for targeted treatments are commonly produced from a single clone.

mAb types are classified according to their source. When naming murine mAbs, they take the "-omab" suffix and are the most immunogenic. When naming chimeric mabs, they take the suffix "-xmab", the humanized ones the "-zumab" suffix, and the "-umab" suffix while naming the completely human-sourced mabs (at least immunogenic) (3).

The target of the most commonly used mAbs in routine practice in oncology is human epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), nuclear factor kappa-B ligand receptor activator, and programmed death-1 (PD-1), which will be discussed under the immunotherapy title and programmed death ligand-1 (PDL-1) (3).

a- Anti-HER-2 monoclonal antibodies

The first use of modern mAb therapy in solid tumors was achieved with the HER-2 mAb trastuzumab (3). Trastuzumab exerts its antitumoral effect by binding to the extracellular domain of the HER-2 receptor, preventing cell-mediated cytotoxicity and ligand-independent HER-2 receptor dimerization (4,5). It is used in HER-2-expressing breast, stomach, and gastroesophageal junction cancers and the most important dose-limiting side effect is cardiotoxicity (6). Pertuzumab binds to HER-2 domain-2, preventing HER-2/HER3 dimerization. The region where trastuzumab and pertuzumab are bound is different from each other and their target properties provide a complementary mechanism for targeted therapy (7). Ado-trastuzumab emtansine is an antibody-drug conjugate that is a microtubule inhibitor fungal toxin emtansine in combination with trastuzumab (4,8,9).

Table 1. Targeted drugs and immunotherapy options

Target therapies		
Monoclonal antibodies	Trastuzumab	Panitumumab
	Ado-trastuzumab emtansin	Bevacizumab
	Pertuzumab	Ramucirumab
	Cetuksimab	-
Tyrosine kinase inhibitors	Sorafenib	Afatinib
	Sunitinib	Osimertinib
	Pazopanib	Crizotinib
	Regorafenib	Ceritinib
	Axitinib	Alektinib
	Erlotinib	Lorlatinib
	Gefitinib	Imatinib
Affecting the proliferation cascade and others	Palbociclib	Olaparib
	Ribociclib	Talazoparib
	Dabrafenib - trametinib	-
	Everolimus	-
Immunotherapies		
Immune chekpoint inhibitors	Pembrolizumab	Durvalumab
	Nivolumab	Avelumab
	Atezolizumab	Ipilimumab
Others	Interferon alpha-2b	CAR-T cell theraphy
	Cancer vaccines	-
	Oncolytic vaccines	-

CARR-T: Chimeric antigen receptor

This molecule has three properties: The anti-HER-2 function of trastuzumab combined with emtansine-induced tissue-specific expression and cytotoxicity (4,10). Margetuximab is an anti-HER-2 antibody that binds with high affinity to both low and high affinity forms of CD16A, an important Fc receptor for antibody-dependent cell-mediated cytotoxicity against tumor cells (11). Trastuzumab deruxtecan (DS-8201), a powerful topoisomerase inhibitor developed in recent years, is a humanized mAbs conjugate with the same amino acid sequence as trastuzumab specifically targeting HER-2. Its efficacy has been demonstrated in metastatic breast cancer patients who have previously received multiple lines of anti-HER-2 therapy (12).

b- Anti-EGFR monoclonal antibodies

Clarifying the biological basis of metastatic colorectal cancer has played an important role in the development of multi-targeted therapies for EGFR and mitogen activated protein kinase (MAPK) pathways, which play an important role in disease progression. In this context, anti-EGFR mAbs, cetuximab and panitumumab, are important therapeutics that block the activation of the MAPK pathway by targeting the extracellular domain of EGFR (13). The efficacy of panitumumab has been demonstrated in the ras-wild type metastatic colorectal cancers, and and cetuximab in ras-wild type metastatic colorectal cancer, head and neck cancers and non-small cell lung cancers. (14). Acneiform skin eruptions are common with anti-EGFR treatments, and dose reduction may be required in case of severe rash (6).

c- Anti-VEGF monoclonal antibodies

VEGF is the most important angiogenic growth factor. The growth of primary and metastatic solid tumors requires robust vascularity, so the VEGF signaling pathway has been an important pathway for chemotherapy. Bevacizumab is a recombinant humanized mAb targeting all forms of VEGF (14). It is indicated in colorectal cancer, non-squamous non-small cell lung cancers, ovarian, cervical and fallopian tube cancers, and primary peritoneal carcinoma (6). Ramucirumab is an IgG1 antibody that targets VEGF-R2. VEGF-A inhibits binding to VEGF-C and VEGF-D and ramicurumab is used in the treatments of advanced gastric and gasroesophageal junction adenocarcinomas, metastatic non-small cell lung cancers and metastatic colorectal cancer (14). Aflibercept is a recombinant fusion protein containing extracellular parts of human VEGF-R1 and 2. It binds to VEGF-A, VEGF-B and placental growth factor. In combination with FOLFIRI treatment, its benefit has been shown in patients with colorectal cancer (15). Besides the common side effects of anti-VEGF treatments such as hypertension and proteinuria, the dose-limiting side effects are thromboembolism, gastrointestinal perforations and bleeding (6).

2- Tyrosine Kinase Inhibitors

Kinases are also called phosphorylases. These transfer a phosphate group from a high energy donor molecule such as ATP to a specific substrate. Protein kinase phosphorylated proteins make functional changes in the target protein (16). Tyrosine kinases play a critical role in the modulation of growth factor signals. Active forms of these enzymes can cause an increase in tumor cell proliferation and growth, an antiapoptotic effect, and promote angiogenesis and metastasis. In addition to growth factors activation, protein kinase activation via somatic mutation is a common mechanism of tumorigenesis. Since all these effects are initiated by receptor tyrosine kinase activation, its inhibitors play a key role in target therapies (2).

TKIs are small molecules and, unlike mAbs, they can easily enter the cell (16,17).

While mAbs can only act on molecules expressed or secreted on the cell surface, small molecule TKIs are largely hydrophobic and can easily enter cells where the receptors can easily interact with intracellular domains and intracellular signaling molecules. As a result, small molecule TKIs can block the activation of various signaling pathways intracellularly (16). Due to the structure of ATP-binding pockets in protein kinases, small molecule agents show high affinity for many members of the receptor tyrosine kinase family, including PDGFR, Raf, EGFR and other targets (15). The multikinase inhibitor profile of some small molecule inhibitors offers the possibility of disrupting several independent biological pathways vital for tumor proliferation and metastasis (18,19).

a- Anti-angiogenic receptor tyrosine kinase inhibitors

In physiological conditions, angiogenesis is under a relatively dynamic homeostasis tightly controlled by pro-angiogenic and anti-angiogenic regulators. In cancer, however, the pro- and anti-angiogenic balance is disturbed and leads to the transition to angiogenesis (20,21). Tumor angiogenesis is a complex mechanism regulated by multiple signaling pathways (20).

Many multi-targeted anti-angiogenic agents have been developed that inhibit multiple signaling pathways (20,22). Sorafenib is a multikinase inhibitor indicated in advanced stage renal cell carcinoma, hepatocellular carcinoma and metastatic differentiated thyroid cancer. Sorafenib targets VEGFR-2, EGFR-3, PDGFRβ, FLT-3, c-kit, RET and RAF. (23-25).

Sunitinib is a multikinase inhibitor similar to sorafenib, but with different specific targets, PDGFRα, PDGFRβ, VEGFR-2 and 3 and c-KIT. It is indicated in the treatment of advanced stage renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors (14).

Pazopanib is an effective multikinase inhibitor against VEGFR-1, 2 and 3, PDGFRα and β, c-KIT receptors (20,26). It is indicated in advanced stage renal cell carcinoma and soft tissue sarcomas that have previously received chemotherapy (8).

Lenvatinib inhibits VEGFR-1, 2 and 3, FGFR-1, 2, 3 and 4, PDGFRα, RET and c-KIT (23,27,28). Lenvatinib is indicated in radioactive iodine refractory differentiated thyroid cancer, advanced stage renal cell carcinoma, and unresectable hepatocellular carcinoma (23,29).

Regorafenib inhibits VEGFR-1, 2 and 3, PDGFRα and β, FGFR-1 and 2, Tie2 and c-KIT receptors (20,30). It is indicated in metastatic colorectal cancer that progressed after standard therapy and in gastrointestinal stromal tumors progressed with imatinib and sunitinib (6).

Cabozantinib is an inhibitor of VEGFR-1, 2, 3, MET, RET, KIT tyrosine kinase and is used in metastatic renal cell carcinoma and medullary thyroid cancer (6). Axitinib VEGFR-1, 2 and 3 targets the PDGFRα and β, c-KIT receptor and is indicated in the second-line treatment of renal cell carcinoma (20,31).

b- EGFR tyrosine kinase inhibitors

Activating EGFR mutations are seen in 15-20% of non-small cell lung adenocarcinomas, and the most common of these mutations are exon 19 deletion and exon 21L858R mutation (32,33). Activating EGFR mutations (except exon 20 insertion) are sensitive to first generation EGFR TKIs (32). Erlotinib and gefitinib, first-generation EGFR TKIs, bind competitively and reversibly to the ATP binding site of EGFR tyrosine kinase. However, after an average of 12 months of response, resistance develops in all patients, including in approximately 50% of the patients with EGFR T790M resitance mutations. Therefore, the 2nd generation EGFR TKIs afatinib, dacomitinib and neratinib were developed not only for the T790M mutation, but also for EGFR activating mutations and wild type EGFR. However, although these agents have been shown to be effective in the T790M mutation *in vitro*, their clinical effects have remained weak (34). Unlike second generation EGFR tyrosine kinases, third generation EGFR TKIs act more specifically and irreversibly against T790M and activating EGFR mutations. Osimertinib is the first to be approved among the third generation EGFR TKIs (34). The most common side effects of EGFR TKIs are rash and diarrhea (14).

c- ALK tyrosine kinase inhibitors

About 85% of lung cancers are non-small cell in histology and only 5-7% of nonsmall cell carcinoma are anaplastic lymphoma kinase (ALK) mutation and approximately 1% *ROS1* gene rearrengement. (35). Crizotinib, a first generation ALK tyrosine kinase inhibitor that binds competitively to the ATP binding site, has been approved in locally advanced and metastatic ALK mutant non-small cell cancers (36).

Due to acquired resistance to crizotinib, the activity of this tyrosine kinase is limited. Secondary mutations in the *ALK* gene are thought to be the most common mechanisms mediating resistance to ALK inhibitors such as crizotinib (36).

Ceritinib, alectinib and brigatinib, which are second generation ALK TKIs developed to overcome crizotinib resistance, are also effective in first-line therapy (35,36). Alectinib treatment has more efficacy with less side effects compared to crizotinib in naive patients (35,37). Lorlatinib, entrectinib and ensartinib are third generation ALK inhibitors developed to overcome second generation inhibitory resistance in ALK positive lung cancer patients (36). Lorlatinib crosses the blood-brain barrier and reaches high intracranial concentrations (38). In patients with previously untreated advanced ALK-positive NSCLC, lorlatinib has a significantly longer progression-free survival and a higher frequency of intracranial response than crizotinib. The incidence of grade 3 or 4 adverse events was higher with lorlatinib than with crizotinib, due to varying lipid levels (39).

d- Anti-HER-2 tyrosine kinase inhibitor

Lapatinib is EGFR (ErbB1) and HER-2 (ErbB2) related small molecule tyrosine kinase and inhibits the downstream signal. This agent is used in combination with oral fluoropyrimidine capecitabine in HER-2 positive metastatic breast cancer who have previously received anthracycline, taxane, and trastuzumab (14). The most common side effect is diarrhea (6).

3- Affecting the Proliferation Cascade and Others

a- Cyclin-dependent kinases (CDK)4/6 inhibitors

Cell cycle abnormalities are common in cancer and have long been a potential treatment target. CDK are critical regulatory enzymes that direct cell cycle transitions and cell division (40,41-44). In recent years, small molecule inhibitors targeting this mitogenic pathway have been developed (45). Among the CDK4/6 inhibitors, palbociclib, ribociclib and abemaciclib are indicated in combination with hormonotherapy (tamoxifen, aromatase inhibitor, and fulvestrant) in metastatic in metastatic hormone

receptor positive HER-2 negative breast cancer (40). Despite similar mechanisms of action, the dose-limiting side effects of these agents are different. Neutropenia, diarrhea and fatigue are dose-limiting for palbociclib, while neutropenia, mucositis, asymptomatic thrombocytopenia, pulmonary embolism, creatinine increase, hyponatremia, and QTc prolongation are dose-limiting side effects for ribociclib (45-47).

b- BRAF/MEK inhibitors

The MAPK cascade is an intracellular signaling pathway involved in the regulation of cellular proliferation and the survival of tumor cells. Several different mutations involving BRAF or NRAS activate the MAPK pathway and cause an increase in cellular proliferation by making an oncogenic effect (48). The activating *BRAF* gene mutation is seen in approximately 50% of melanomas. V600E mutation is seen in more than 70% of BRAF mutations and V600K mutation is seen in 10-30% (49). Inhibition of the MAPK pathway with the combined use of BRAF and MEK inhibitors has been an effective treatment option in the treatment of BRAF mutant melanoma (50). Trametinib is the first MEK inhibitor approved for the treatment of BRAF mutated metastatic melanoma that has not been previously treated with BRAF inhibitors, and is approved in combination with the BRAF inhibitor dabrafenib. In addition, cobimetinib in combination with another BRAF inhibitor vemurafenib is another MEK inhibitor approved for the treatment of BRAF mutated metastatic melanoma. The MEK inhibitor binimetinib in combination with the BRAF inhibitor encorafenib is under clinical development (48).

c- Phosphoinositide 3-kinase (PI3K) inhibitors

The PI3K/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway plays an important role in cell proliferation, cell life and angiogenesis. PI3K mutations are often seen in estrogen receptor (ER) positive breast cancer. Specifically, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutations encoding the alpha isoform of the catalytic subunit of PI3K are detected in more than 40% of ER-positive breast cancer (51). Previous studies evaluating fulvestrant in combination with pan-isoform PI3K inhibitors (buparlisib and pictilisib) or beta isoform protector taselisib have shown limited improvements in progression-free survival in patients with endocrine-resistant disease, but due to their toxicity (gastrointestinal side effects, transamin increase and hyperglycemia) their therapeutic usage is limited (52-56). The effectiveness of alpha isoform-specific PI3K inhibitor alpelisib, independent of the previous use of CDK4/6 inhibitors, in combination with fulvestrant in hormone receptor positive HER-2 negative and PI3K mutant breast cancer patients was shown in the SOLAR-1 study, and the efficacy after the use of CDK 4/6 inhibitors by its anticipated side effects was shown in the BYLieve study (51).

d- Mammalian target of rapamycin inhibitors

mTOR is an intracellular protein that has a central role in cellular function. It acts as a nutrient sensor and mediates downstream of receptor tyrosine kinases that control cell growth, protein synthesis, autophagy, and angiogenesis (57). Dysregulation of the mTOR pathway is associated with cancer and other diseases (58). Everolimus, one of the mTOR inhibitors, is used in combination with exemestane in hormone receptor positive, HER-2 negative breast cancer, and used as monotherapy in gastrointestinal neuroendocrine tumors, renal cell carcinoma, renal angiomyolipoma and tuberous sclerosis complex. Temsirolimus is indicated in the treatment of advanced stage renal cell carcinoma (6).

e- Smoothened (SMO)/hedgehog inhibitors

Advanced basal cell carcinoma (BCC) constitutes a small proportion of BCCs and is not suitable for standard treatments due to low efficacy, high risk of recurrence and excessive morbidity. The impact of the sonic hedgehog (Shh) pathway in the development of BCC has led to the development of systemic Shh pathway inhibitors that contribute to new treatment options and survival in patients with advanced BCC (59).

Vismodegib and sonidegib, used in BCC treatment, show their activity by binding and inhibiting SMO, which is a transmembrane protein in the hedgehog pathway (6).

f- Poly (ADP-ribose) polymerase (PARP) inhibitors

Heterozygous germline mutations in the *BRCA1* and *BRCA2* genes result in a high risk of breast cancer (up to 85% lifetime risk), ovarian cancer (10% to 40%) and a significantly increased risk of pancreatic, prostate, and male breast cancer (60). PARP enzymes are involved in normal cell homeostasis such as DNA transcription, DNA repair, and cell cycle (6). BRCA1 and BRCA2 mutation tumors are sensitive to PARP inhibitors because they have a specific DNA repair defect (61). It has been suggested that PARP1/2 expression levels may be the biomarker for the inhibitory response. While olaparib and veliparib are highly selective inhibitors of PARP1 and PARP2; niraparib, rucaparib and talazoparib are general PARP inhibitors (54). PARP inhibitors can cause various cytopenias. While olaparib, rucaparib and talazoparib can cause severe anemia, niraparib can cause thrombocytopenia more frequently besides anemia (62).

IMMUNOTHERAPY

Immunotherapies are therapies that strengthen the immune system by regulating the immune microenvironment, thereby allowing immune cells to be protected from attacking tumor cells (63). Compared to conventional cancer treatments, cancer immunotherapy contributes significantly to life expectancy and quality of life. Immunotherapy has proven itself in many types of cancer, from the metastatic stage palliative to (neo) adjuvant therapy, by the molecules and clinical studies developed in the last 10-15 years (63). Immunotherapies in cancer treatment were highlighted as "publication of the year" in Science magazine in 2013 and "progress of the year" in 2015 by the American Society of Clinical Oncology (64-66). Immunotherapy strategies consist of antibodies or recombinant proteins that co-stimulate or block cells, named as cancer vaccine, oncolytic viruses, *ex vivo* activated T-cell and natural killer (NK) cell transfer, and immune checkpoint inhibitors (67).

Interleukin-2, the first immunotherapy used in human cancers, is a T-cell growth factor (68). Although its use after immune checkpoint inhibitors decreased significantly, high-dose bolus IL-2 provided a long-term response rate in a small proportion of patients with melanoma and renal cell carcinoma, and showed that the immune system could destroy cancer cells (69).

Aldesleukin is a human recombinant IL-2 analogue. The most important side effect of IL-2 therapy is that it causes capillary escape syndrome, causing fluid leakage into visceral organs and dysfunction (68).

a- Interferon Alpha-2b

Interferon alpha-2b activates certain enzymes by binding to the specific membrane receptor on the cell surface and exerts immunomodulatory effects such as suppressing cell proliferation, increasing phagocytic activation of macrophages, increasing cytotoxic effect of lymphocytes to target cells, and decreasing virus replication in virus-infected cells. Long-acting pegylated versions of interferon are effective in melanoma, kaposi sarcoma, follicular lymphoma and hairy cell leukemia (6).

b- Cancer Vaccines

Cancer vaccines has antitumor activity by providing specific stimulation of the immune system using tumor antigens. Different vaccine strategies have been developed (70). Compared to standard cancer treatments, tumor vaccines theoretically have many advantages. It is possible to create specific cancer therapy with vaccine therapy. Long-lasting anti-tumor responses can be achieved by stimulating tumor-specific memory T-lymphocytes. The incidence of side effects of cancer vaccines in individuals is rare. Among these side effects; transient fever, flu-like symptoms or autoimmune reactions are included (71). Cancer vaccines include antigen vaccines, anti-idiotype vaccines, dendritic cell vaccines, genetic vaccines and tumor cell vaccines (71).

Currently the only vaccine-based therapy approved for cancer treatment is sipuleucel-T. Sipuleucel-T is a vaccine treatment produced by autologous dendritic cell engineering targeting prostatic acid phosphatase used in castration resistant prostate cancer (72). It is obtained by culturing the peripheral blood antigen presenting cells (monocytes and lymphocytes) taken from the patient by plasmapheresis with prostate cancer cell protein PAP and granulocyte-macrophage colony-stimulating factor. It is injected back to the patient after purification (73).

c- Oncolytic Viruses

Oncolytic viruses mediate antitumor effects in a variety of ways. Viruses can infect cancer cells to stimulate the presentation of tumor-associated antigens, stimulate a "distress signal" to the less immunolerant tumor microenvironment, and serve as transduction tools for the expression of immune modulatory cytokines (74).

Talimogene laherparepvec is a live attenuated herpes simplex type 1 virus, genetically modified, developed to provide antitumor response in tumor cells through selective viral replication and stimulation of antitumor immunity. It is the first oncolytic virus approved for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in malignant melanoma recurring after the first surgery (75).

d- Chimeric Antigen Receptor (CAR) T Cell Therapy

CAR-T cell therapy provides a great advantage in personalized cancer treatment, in which the patient's own T-cells are genetically modified to produce synthetic receptors that bind to the tumor antigen. CAR-T cells are then infused into the patient to attack and destroy chemotherapy resistant cancer. CAR-T cell therapy has dramatic response and complete remission rates in B-cell hematologic malignancies. CAR-T cell therapy is one of the first successful examples of synthetic biology and personalized cellular cancer therapy (76).

e- Immune Checkpoint Inhibitors

Immune checkpoints are located on the surface of T-cells or tumor cells as effective targets to inhibit the overactivation of T-cells. Under normal conditions, immune control proteins are intended to prevent autoimmune disease damage by suppressing the excessive immune response, but when the tumor develops,

they inhibit the recognition of the tumor cell by T-cells and weaken the immune system's ability to recognize and destroy tumor cells (77).

Cytotoxic T lymphocyte antigen (CTLA-4) acts on the surface of CD4 and CD8 T lymphocytes by binding to the co-stimulatory receptors CD80 and CD86 (B7-1 and B7-2) on the antigen-presenting cell surface with a higher affinity than the T-cell co-stimulator (78).

The interaction of CTLA-4 with these ligands inhibits the T-cell response by showing a braking effect (79). Ipilimumab, one of the anti-CTLA-4 antibodies, is an immune checkpoint inhibitor of which first clinical studies have been published and its contribution to survival in metastatic melanoma has been proven (80). PD-1 is a transmembrane protein expressed on the surface of T-cells, B-cells, and NK cells.

PD-1 binds to ligand 1 and 2 (PDL-1 and PDL-2) and acts as an inhibitor. The interaction of PD-1 with PDL-1/2 directly inhibits tumor cell apoptosis, promotes peripheral T effector cell depletion and supports the transformation of T effector cells into Treg cells (81,82). PD-1/PD-L1 mAbs are used in melanoma, non-small cell lung cancers, head and neck cancers, Hodgkin's lymphoma, urinary epithelial cancer, gastric cancer, kidney cancer, liver cancer and many other cancers. Because these antibodies are more selective, they have fewer side effects and are more reliable than CTLA-4 inhibitors (77,83-87). PD-1 mAbs are pembrolizumab, nivolumab, cemiplimab, toripalimab, and sintilimab. PDL-1 mAbs are atezolizumab, avelumab, durvalumab and pidilizumab (77).

Immunotherapy combinations such as ipilimumab and nivolumab are associated with increased toxicity in melanoma studies, despite a greater response rate (68). Immune checkpoint inhibitors can cause a large number of non-specific T-cell activation-related and general immunological side effects. Many autoimmune events can occur, but rheumatological tests are usually negative. Mostly the skin, gastrointestinal system, liver, endocrine organs and lungs are affected, but immune-related side effects may develop in all organs and the main treatment is corticosteroids (68). The response pattern to immune checkpoint inhibitors may differ from the response to conventional chemotherapy or molecular targeted therapies (88). Patients may develop a temporary worsening of the disease, which occurs with the progression of known lesions or the emergence of new lesions before the disease is stabilized or the tumor regresses, and this phenomenon, which we call pseudoprogression, may be confused with real progression. However, these delayed responses are not usually observed in patients with symptomatic worsening, so continued treatment is not recommended in patients with symptomatic worsening (89). For all these reasons, instead of response evaluation criteria in solid tumors (RECIST) used for conventional therapies, a revised response and evaluation criteria was described for immune check point inhibitors, namely immune related response criteria (iRECIST)(68).

CONCLUSION

With a better understanding of the molecular biology and genetics of cancer, serious developments have been made in cancer treatment especially in recent years. Numerous new targeted molecules and immunotherapy approaches have been found to provide higher antitumor effect with fewer side effects, and they have started to enter our clinical practice. With targeted therapies and immunotherapies, there is a significant increase in the life expectancy of patients. Studies on drugs and immunotherapies that target many new molecules are still ongoing, and today we are fighting cancer with weapons much more powerful than conventional therapies. Recent advances in cancer treatment promise even greater hope for the future.

Ethics

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Authorship Contributions

Surgical and Medical Practices: F.Y., B.Ö., Concept: F.Y., B.Ö., Design: F.Y., B.Ö., Data Collection or Processing: F.Y., B.Ö., Analysis or Interpretation: F.Y., B.Ö., Literature Search: F.Y., B.Ö., Writing: F.Y., B.Ö.

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