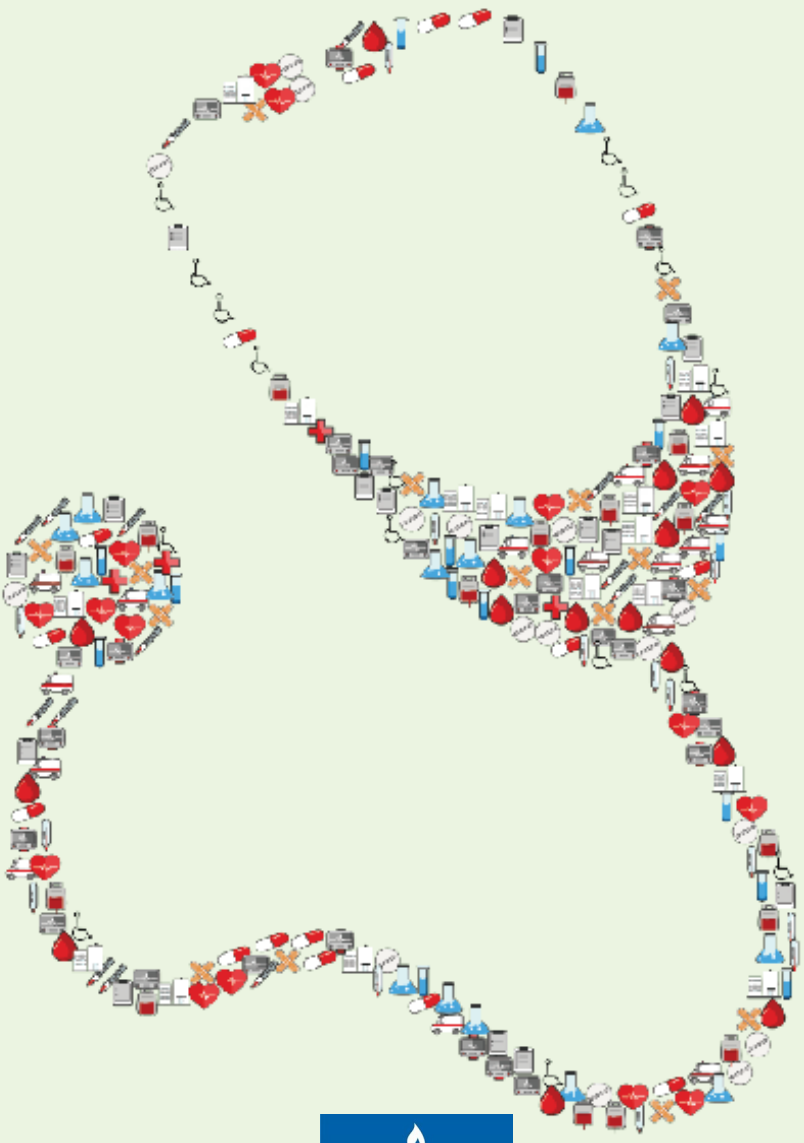
CANCER CHEMOTHERAPY

Assoc. Prof. Dr. İbrahim AKTAŞ



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PREFACE

This book was written to fill the shortage of books for midwifery - nursing and associate degree health programs. The topics covered in this book include the current status of drugs and have the ability to be a resource in cancer courses. We hope that this book will be a resource for midwifery, nursing and associate degree health programs, and for the professors who teach cancer courses and the students who take this course.

Assoc. Prof. Dr. İbrahim AKTAŞ

THANKS

I would also like to thank the board of directors and staff of İKSAD Publishing House, who encouraged me to write a book and also contributed to the preparation of the book.

Assoc. Prof. Dr. İbrahim AKTAŞ

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1. BASIC INFORMATION IN CANCER CHEMOTHERAPY

Cancer is the uncontrolled reproduction of cells and their metastasis to other tissues through blood and lymph (Bilgiç & Aktaş, 2021). Cell division and functions are under the control of genes. The genes in the chromosomes are packaged and the chemical and physical changes here affect the function of the cell. Although DNA repair systems try to repair the damage in the gene, it is not always successful. In this case, the faulty or incomplete production of proteins under the control of genes causes deterioration in the functions of the cells. Epigenetic modifications that change the function of the gene are; methylation, phosphorylation, acetylation and ribosylation. These can also occur in the form of insertions, deletions and inversions in all or a large part of the chromosomes. These are oncogenes, tumor suppression and DNA repair genes that play a role in the development of cancer. In this case, proto-oncogenes; They can become oncogenes (Erk, RAS and MYC genes) by being activated with mutations, increased gene duplications and chromosomal rearrangements. The gene groups that control cell division and proliferation, initiate DNA repair in case of damage and induce apoptosis in case of failure of repair are called tumor suppressor genes. The most researched gene is TP53. The improper separation of chromosomes; point mutations, deletions, mitotic recombinations and epigenetic silencing cause the tumor suppressor gene to lose its function. This situation causes the loss of control in the cell cycle and ultimately carcinogenesis. The other group of genes; DNA repair genes, which are genes that restore the function

of the gene by attracting the proteins necessary for repairing defective DNA to that area. Another function of the repair gene; ensures that the cells are destroyed by necrotic or apoptotic pathways in the event of failure of repair. However, loss of function in these gene groups is frequently observed in cells becoming cancerous. The most well-known DNA repair gene is the breast cancer gene. Breast cancer occurs when this gene loses its function. When cells receive external stimulation, they divide, multiply and grow. Incoming stimulations enter the cell, pass to the nucleus and start the process. Before cell division; it checks the environment and starts growth if there is nutrition, space and a suitable environment. These cells grow until they reach a certain size and number, and growth stops when they touch each other. When one of the elements of the cell or the DNA is damaged, the cells divide and stop growing. They enter the G0 phase to repair. They continue their life by entering the circulation during the repair of damaged cells. If they cannot be repaired, they are sent to apoptosis or the immune system destroys those cells (Aktaş et al., 2024a). Characteristics of cancerous cells.

• Receptors around the cell receive signals more frequently than normal cells

• They have their own signaling systems that allow uncontrolled reproduction.

• While normal cells use all kinds of nutrients, cancer cells only use glucose formed from glycolysis. They take sugar from the blood 100 times more than normal cells and produce lactate to create energy.

• They affect the stroma to receive the necessary oxygen and nutrients and create a new vascular system.

• They replicate and multiply indefinitely by fixing their telomeres or preserving the telomerase function.

• They enter the circulation, settle in a new location and initiate cancer.

• They can escape apoptosis.

• They are not epigenetically and genetically stable.

Cancer cells resist harsh conditions by living with little oxygen and nutrients. Healthy cells live in a certain area. Cancer cells, on the other hand, can live by multiplying without being fixed in a place (Baykara, 2016). The main principle in chemotherapy is to stop the reproduction of cancer cells and destroy them without harming healthy cells. Antineoplastics affect healthy tissues such as intestinal epithelium, hair follicles, and bone marrow stem cells that are proliferative along with the tumor. The therapeutic indexes of antineoplastics are low compared to antimicrobial drugs and have more side effects. In addition, they affect organs such as the liver and kidneys, which reproduce slowly. These drugs are effective on dynamic events related to cell reproduction. If the tumor has not spread too much, the tumor is surgically removed with neighboring lymph nodes and radiotherapy is applied. However, if the tumor is widespread, the only solution is anticancer chemotherapy. In these patients, the risk of infection due to immune deficiency is high (Gür & Aktaş, 2022).

1.1. Etiology of Cancer

1.1.1. Smoking: Tobacco use is a preventable cause of cancer. Reducing use reduces the incidence of lung and laryngeal cancer. Cigarette smoke contains approximately 8000 carcinogenic compounds, more than 70 of which are carcinogenic. Increasing inflammatory markers in the circulation, DNA methylation dysregulation, airway gene expression mutations, oral microbiota change, specific mutations and Y chromosome loss are the precursors of cancer (Arslan et al., 2020).

1.1.2. Infectious Agents

• Carcinogenic bacteria; *H. Pylori*

• Viruses; hepatitis C and B, Epstein-Barr Virus, Kaposi sarcoma agent human herpes virus-8, human papillomavirus (HPV) subtypes, T cell lymphotropic virus type 1 and human immunodeficiency virus-1.

• 13 HPV subtypes are responsible for cancer, HPV 16 and HPV 18 are responsible for 70% of cervical cancer.

• Epistein Barr Virus; causes Burkitt lymphoma and naso pharyngeal cancer, Hodkin lymphoma, stomach cancer, multiple sclerosis.

• Macroparasites; schistosoma haematobium, opisthor chis, viverrini, clonorchissinensis.

• Safe sexual intercourse (marriage), circumcision for men, restriction of tobacco use and vaccination for cervical cancer and oropharyngeal cancer are protective (Arslan et al., 2020).

1.1.3.Alcohol (methanol): Increases DNA methylation and serum levels of endogenous estrogens. Changes the reactive oxygen radicals (ROS) and insulin-like growth factor 1 pathway. Increases cancer by acting as a solvent for the penetration of environmental carcinogens (tobacco) into the cell. In addition, increasing intracellular ROS and depleting the antioxidant glutathione (GSH) are obvious effects of ethanol (Aktaş & Gür, 2021; Arslan et al., 2020).

1.1.4. Ultraviolet (UV) Radiation: Triggers ROS formation. Increases the frequency of DNA damage and mutations. Also contributes to immunosuppression by creating lipid peroxidation. In addition, the risk of skin cancer increases due to the effect of UV as a result of increased life expectancy. As a result, non-melanoma skin cancer increases even more in the elderly. Cancer incidence can be reduced by avoiding unnecessary sun exposure and taking the necessary precautions (Arslan et al., 2020).

1.1.5. Diet and Nutrition: A diet rich in carotenoids (vegetables and fruits) reduces the risk of breast cancer (Bilgic et al., 2021). Processed red meat and low vitamin D levels in the diet increase the incidence of chlororectal cancer. In a diet devoid of animal fats, the incidence of prostate cancer is low (Aktaş et al., 2020a; Arslan et al., 2020).

1.1.6. Obesity and Exercise: After menopause; the incidence of breast, chlororectal, endometrium, kidney, liver, esophagus, pancreas and gallbladder cancer increases. In contrast, regular physical activity reduces the incidence of bladder, breast, colon, endometrium, kidney, stomach cardia and esophagus adenocarcinoma (Arslan et al., 2020; Bilgiç et al., 2016).

1.1.7. Environmental Factors: There is a direct relationship between air pollution and environmental and chemical wastes in drinking water and cancer. In addition, outdoor air pollution containing particles smaller than 2.5μm increases the risk of lung cancer.

1.1.8. Drugs: Oral contraceptives increase the incidence of breast and cervical cancer, while reducing the incidence of ovarian and chlororectal cancer. Aspirin use reduces the risk of chlororectal cancer.

1.2. Screening Programs in Turkey

1.2.1.Breast screening program

• Women between the ages of 20-40 should examine themselves every month.

• They should have breast screening tests every 3 years.

• Women between the ages of 40-69 should examine themselves every month. They should also have a breast examination at a health institution once a year. They should also have a mammogram every 2 years and go to the hospital if they have any findings.

1.2.2. Colon cancer screening program:

• In suspects between the ages of 50-70, a fecal occult blood test (GGT) should be performed every 2 years,

• Colonoscopy is recommended every 10 years.

• Those with a history of colon cancer should start at the age of 40. In colonoscopy, benign polyp tumors should be detected in GGT positive patients and cancer should be prevented.

1.2.3. Cervical screening: HPV and smear tests are performed every 5 years for women between the ages of 30-65 (Arslan et al., 2020).

1.3. Factors Related to Tumor-Drug Interactions

• Drugs reduce the tumor to a certain extent. However, all malignant cells must be killed in the elimination of the tumor. They reproduce rapidly, even in the vitality of a single cell, and recreate the tumor.

• The specificity of the cell's reproductive phase limits the effectiveness of drugs.

• The rate of tumor cell growth changes the effectiveness of the drug. Fast-growing cells are more sensitive to most drugs than slow-growing ones. In addition, drug sensitivity decreases as the tumor grows.

1.4. Limiting factors for antineoplastics: Most antineoplastics kill malignant cells by preventing their growth and proliferation with

their cytotoxic effects. Although there are some tumors where antineoplastics provide cure, success is not possible in most metastases.

1.5. Tumor biology and tumor-drug interaction factors

1.5.1. Killing cells with drugs: The fractional cell killing assumption suggests that a cytotoxic cancer drug applied for a period and dose and not specific to the period kills not a fixed number of cells in the tumor but a fixed rate, and that this rate is independent of the absolute cell number. According to this assumption, the decrease in the number of malignant cells observed after drug application is exponential. This exponential decrease is one of the reasons why antineoplastics should be repeated in cycles and used in combination. However, considering the proliferation of the tumor mass during treatment intervals, it is not possible to destroy all cells with drugs. The heterogeneity of human tumor tissue limits the validity of this assumption. In the heterogeneity of tumors, clones that are resistant to drugs reduce the success of treatment. In the application of period-specific antineoplastics such as methotrexate, there is a plateau-type decrease in the number of malignant cells. When such antineoplastics are applied, they kill cells in a certain period, such as the S period. They have no effect on cells in other periods of the cycle. Antimicrobial chemotherapeutics also act through similar kinetics. The fact that antineoplastics are less selective and cannot be applied in effective doses, and that the immune system cannot perform the same success against tumors as it does against an infection, leads to the difference in success between the two treatment approaches.

1.5.2. Specificity of antineoplastics to cell cycle phase: Some drugs are effective in a period of the cell cycle in reproductive cells. These are called period-specific drugs. They are effective in the reproductive process such as DNA formation, mitotic spindle development and transcription of DNA. Other drugs cause direct DNA damage and have a lethal effect. These are called period-nonspecific drugs. Hormonal drugs are period-specific drugs and block Gj/S transition in cells with hormone receptors.

1.5.3. Tumor proliferation rate: Its indicator is called the reproduction criteria or doubling time. The reproduction criteria are the ratio of the number of cells in the tumor that are dividing to the total number of cells. Doubling time is the name of the time it takes for the tumor to double in volume or cell number. The doubling time of the tumor is between 7 days and a few years. For example; This period is short in tumors such as high-grade lymphoma, acute leukemia, testicular and small cell lung cancer. This period is long in some types of stomach, colorectal, small cell lung and prostate cancer and skin cancer-like tumors. In the second group of cancers, the tumor cell cycle is long and a significant portion of the cells are in the resting (G0) phase of the cycle. Rapidly growing tumors are more sensitive to most antineoplastics, especially antimetabolites and antineoplastic antibiotics, than slow-growing tumors. Accordingly, large tumors will be less sensitive to chemotherapy. When the tumor mass is small, sensitivity to antineoplastics is even more pronounced.

These form the basis of two treatments:

1. Chemotherapy for micrometastatic disease following local treatment of the tumor,

2. Reduction of tumor volume by surgery. In both treatments, the growth fraction in the remaining microscopic and macroscopic tumor after treatment will increase and the effectiveness of the chemotherapeutics will become apparent.

1.6. Pharmacology and pharmacokinetics of the drug: The concentration of antineoplastics in the tumor is determined by the route of administration and pharmacokinetics of that drug. For example; most chemotherapeutics cannot cross the blood-brain barrier and enter the central nervous system (CNS). Drugs that cross the blood-brain barrier are nitrosoureas, epipodophyllotoxin and procarbazine derivatives (Bilgiç et al., 2023a). With this feature, methotrexate should be administered intrathecally to prevent CNS recurrences in acute lymphoblastic leukemia. In the treatment of superficial bladder cancer; BCG vaccine, interferon or some cytotoxic drugs are applied directly into the bladder cavity. In order to increase the drug density in the tumor tissue, organ or extremity perfusion method is applied. In some tumors, high dose drug should be applied in order to obtain intracellular effective drug density. For example, in acute lymphoblastic leukemia, methotrexate; when applied in high doses, increases the formation of long-chain polyglutamates in the cell and activates the treatment. High dose methotrexate ensures that the drug passes through the blood-brain barrier sufficiently. According to these conditions, the dose of the drug

should be adjusted according to the body surface volume of the person. One of the dose-limiting factors is myelotoxicity (bone marrow toxicity). Among the hormones; most antineoplastics are myelotoxic except for bleomycin, vincristine, cisplatin and asparaginase. The dose-limiting side effect for methotrexate, fluorouracil, dactinomycin and doxorubicin is mucositis. For bleomycin, it is pneumonitis and lung fibrosis. For daunorubicin and doxorubicin, it is cardiomyopathy. For vincristine, it is peripheral neuropathy. For cisplatin, it can be considered as nephrotoxic effect (Bilgiç et al., 2024).

1.6.1. Approaches that enable high-dose chemotherap:

1.6.2. Antidote application that reduces toxicity without changing antineoplastic activity: Application of high-dose methotrexate with folinic acid.

1.6.3. Local high-density drug application to the area where the tumor is located:

• Hepatic artery perfusion in liver tumors,

• Extremity perfusion using the arteries of that region in extremity tumors,

• Intraperitoneal or intrapleural drug application in tumors that have spread to the peritoneal or pleural space.

• Intralesional drug injection in solid tumors.

1.6.4. Hematopoietic growth factors: Filgrastim, lenograstim and pegfilgrastim are used for dose-limiting myelotoxicity in

antineoplastics. These are administered to patients 24-48 hours after chemotherapy that causes neutropenia. This application can reduce the depth and duration of neutropenia. It can also ensure that chemotherapy is administered at the planned time,

1.6.5. Stem cell transplantation and high-dose chemotherapy: In relapsed lymphomas and other tumors, autologous stem cell transplantation and high-dose chemotherapy are recommended. The aim here is to minimize the myelotoxic effects of chemotherapeutics. Allogeneic stem cell transplantation is a type of immunotherapy.

1.6.7. Targeted drug delivery systems: It is done by binding the antineoplastic drug to a specific monoclonal antibody. In addition, the drug solution is directed to the target by trapping it in liposomes with either a single or specific antibody attached.

1.7. Drug resistance: The limiting factor of antineoplastic treatment is resistance. Some tumors do not respond to chemotherapy, this is primary resistance. Resistance may also develop in chemotherapy, this is called secondary resistance. The spectrum of activity in cancer types that are sensitive to chemotherapy is described as the drug group to which the tumor is sensitive. The heterogeneity of the tumor and the death of cells sensitive to chemotherapy create a tumor that shows acquired drug resistance. In preventing drug resistance; drugs that act alone in that tumor, but have different side effects and mechanisms of action are used in combination. If a single drug is necessary, the drug should be given in sufficient doses and for a sufficient period of time.

1.7.1. Mechanisms of resistance to antineoplastics

• Decreased entry of the drug into the cell by the cancer cell,

• Increased production of the target enzyme or decreased affinity for the drug. For example, resistance to methotrexate, amplification of the gene encoding the dihydrofolate reductase enzyme and increased production of the mRNA that synthesizes this enzyme.

• Decreased bioactivation of the drug to its active metabolite.

• Increased inactivation of the drug.

• Acceleration of repair of damage caused by the drug in the cancer cell DNA.

• Activation of backup pathways in pyrimidine and purine biosynthesis. Also increased production of normal pathway enzymes.

• Increased production of P-glycoprotein, the pump protein that expels some drugs from the tumor cell in an energy-dependent manner, and increased synthesis of other multidrug resistance proteins.

• Resistance in the topoisomerase II enzyme.

• Stimulation of glutathione synthesis and glutathione-S-transferase enzyme production in the cell.

• Decrease in the tendency of the cell to apoptosis. Angiogenesis (neovascularization) occurs from the earliest stages of tumor development. In rapidly growing tumors, vascularization may be inadequate and necrosis may develop. This situation reduces the drug's

access to the center of the tumor mass. In addition, hypoxia in this area reduces the effectiveness of some antineoplastics.

1.8. Factors related to the patient:

1.8.1. General condition of the patient: Chemotherapy success is high and side effect development is low in those who continue their daily functions.

1.8.2. Patient's immunity: In those with normal immunity, chemotherapy responds better than in those with abnormal immunity. Antineoplastics also cause immune deficiency. Therefore, drugs are given at sufficient intervals. Chemotherapy and radiotherapy in patients reduce the effectiveness of drugs due to the development of immune deformation. Some neoplasms (lymphomas) cause immunosuppression. In addition, antineoplastics given for treatment also suppress immunity.

1.8.3. Previous chemotherapy and radiotherapy: Previous chemotherapy may lead to a decrease in bone marrow reserve and an increase in toxicity in subsequent applications. Some drugs cause cumulative bone marrow, cardiac and renal toxicity. In tumors that are likely to be treated with chemotherapy, initial treatment should be at the optimum dose intensity and within a certain range. In curative chemotherapy, supportive measures such as erythrocyte, platelet and less leukocyte transfusion, hematopoietic growth factor, antimicrobial chemoprophylaxis and hyperalimentation should be taken against side effects. In tumors where the probability of success in chemotherapy is low; treatment should be palliative and when complications occur or

the probability of complications is high, the doses of chemotherapeutics should be reduced appropriately. In those who have received radiotherapy before; pelvic irradiation increases the sensitivity of the bone marrow, mediastipal irradiation increases the sensitivity of the heart, and CNS irradiation increases the sensitivity of the brain to subsequent treatments.

1.8.4. Other factors: The person's age, race, gender, organ status and other disorders accompanying cancer. The effectiveness of the drug may decrease with age and the sensitivity to toxic effects may increase. In some organ failures; a drug may be contraindicated, and changes in hematological and biochemical parameters may require dose reduction or discontinuation of the drug (Tanbek et al., 2017).

1.9. Cell cycle: The cell divides and forms two cells, and goes through 4 consecutive periods. These are called Gp S, G2 and M (mitosis) periods. There may be a G0 period in between. The resting period in some normal cells (such as neurons and striated muscle cells) continues throughout the life of these cells after mitosis. The few normal cell types that proliferate rapidly; bone marrow, gastrointestinal epithelial layer, germ cells in the testis and rapidly reproducing tumor cells divide continuously without a resting period.

1.9.1. Gj (preparation for DNA synthesis) period: The preparation period for S phase; It is the period in which the enzymes (thymidine kinase, DNA polymerase and dihydrofolate reductase), histones and nucleotides, which are the necessary elements for DNA strand synthesis and chromosome formation, are synthesized. It is the

phase whose duration varies the most in tumor types. The reproduction rate of the tumor cell is determined. In some slowly growing tumors, the tumor cell enters the G0 period from mitosis. In tumors and non-tumor normal cells, various stimuli are given to enter a cell in G0 into the death period. The most important of these are the chemical stimuli given by various growth factors (GFs) present in the tissue. The main GFs are growth factors; vascular endothelial growth, epidermal growth, fibroblast growth, platelet-derived growth factor from platelets. GFs stimulate membrane receptors related to kinases and "mitogen-activated protein kinase" coupled to other receptors in the membrane, thus accelerating cell proliferation by increasing the transcription of the relevant genes and the synthesis of the building block molecules accordingly. An important example of the transition of normal cells from the resting phase to the Gj period is the tissue repair event initiated by the increased synthesis of GFs as a result of tissue injury.

1.9.2. DNA synthesis or replication phase (S period): DNA double-strand is opened and a new DNA strand is formed according to the template formed by each strand, and this phase generally lasts for 4-24 hours.

1.9.3. Mitosis preparation phase (G2 period): This is the phase in which the mitosis spindle develops, where mRNAs and the proteins that match it are produced. It lasts for approximately 2 hours in normal cells and tumor cells.

1.9.4. Mitosis phase (M period): This is the phase in which cells that contain two copies of double-stranded DNA strands in the S phase

separate into two cells with the mitosis event in which each of these copies is shared. Mitosis consists of 6 stages and lasts for approximately 1 hour.

1.10. Positive and negative regulators of the cycle: The role of growth elements and their receptors in initiating the transition from G0 to G was explained. These elements activate and control the biological system called "positive cell cycle regulators" (PHSD), which is not only involved in the transition from G0 to G, but also in initiating and maintaining the transition to the following periods. The mediator molecules of the PHSD system, which stimulate the cell to divide faster, are proteins that form two protein families called cyclins and cyclin-dependent kinases. Later, poloS (synthesis, replication) periods of cell proliferation and checkpoint kinases also play a role in the cell cycle. The transition from one period of the cell cycle to the next is carried out through these molecules. Cyclins bind to sbks and stimulate them. They enable them to phosphorylate and activate (and inhibit some) substrate molecules that play a role in the execution of the cell cycle. There are 8 main groups of cyclins. The ones that play an important role in cell cycle control are cyclin A, B, D and E. Each cyclin affects one or two specific sbk molecules. For example, sbk 1 and 2 are stimulated by cyclin A, and sbk 4 and 6 are stimulated by cyclin D. After cyclins combine with sbks and activate them, they are destroyed in the cell and are produced for one-time use. There are also "cell cycle negative regulators" that affect the cell cycle in the direction of slowing down or stopping division. An important part of the mediator molecules that make up this system are sbk inhibitors (such as p21, p27 and p57

proteins) that bind to sbk molecules and inhibit them. Another part is kinase inhibitor proteins (such as p15, p16 and p19). Inhibitor proteins exert their suppressive effects on the cell cycle in two places. These places are between the Gj period and the S period and between the G2 period and the M period. The first is called checkpoint 1 and the second is called checkpoint 2. The p53 gene, which is an important division inhibitor gene, performs the inhibition at checkpoint 1 through the p21 protein it synthesizes. The Rb protein, which is outside the types of inhibitor proteins listed above, stops division by blocking the transition from the Gj period to the S period at checkpoint 1. It does this by binding to and blocking the "E2F transcription factor" responsible for the expression of the gene encoding cyclin E and A, which will be required for the synthesis of the enzymes that take part in the S period.

1.11. Other events accompanying cell division: In division, the interaction between the cell and the matrix of the tissue inside (extracellular ground substance) and matrix metalloproteinases secreted from the cell is important in facilitating division and making room for the new cells that emerge. The main substances that make up the extracellular matrix are proteoglycans, collagens and fibronectin molecules. These building blocks that make up the matrix and the metalloproteinases that break them down are synthesized by cells under the stimulating effect of growth factors and secreted into the extracellular space. There is an interaction between transmembrane receptors called integrins, which consist of α and β subunits located on the membranes of cells in the tissue, and fibronectin molecules in the matrix. Activation of growth factor receptors and integrin receptors

located on the membranes of cells in the matrix activates adaptor proteins (APs) and local adhesion kinase next to these receptors, stimulating the kinase pathway within the cell. There is an interaction between the growth factor and integrin pathways in the form of mutual communication. As a result of the activation of these two transduction pathways, the signal transmitted to the nucleus activates early response and then delayed response genes. Delayed response genes are genes that control the expression of the "positive regulators and negative regulators" of the cell cycle. Interleukins also play a role in the expression of matrix-forming proteins and matrix-degrading metalloproteinases, as well as growth factors. Growth factors initiate the cell cycle in tissue cells and cause the inactive metalloproteinase precursors from the cells to be secreted into the medium and converted into active forms. Metalloproteinases also increase the secretion of growth factors from tissue cells that secrete them. The effect of metalloproteinases is suppressed by tissue metalloproteinase inhibitors. Metalloproteinases and the matrix destruction they cause in the context of tumors; allows the tumor to grow and invade the tissue. This matrix destruction also plays a role in metastasis and also in tissue destruction in degenerative diseases such as rheumatoid arthritis and osteoarthritis. Another event that accompanies tumor development in tissue is angiogenesis, the formation of blood vessels. As tumor cells divide and proliferate, new capillaries are formed from small blood vessels in the tissue under the stimulating effect of various growth factors and cytokines, especially vascular endothelial growth factor.

1.11.1 Vascular endothelial growth factor causes angiogenesis:

• Initially, vasodilation caused by nitric oxide formation,

• Destruction of the vascular basement membrane by increased production of metalloproteinases,

• Formation of capillary buds as a result of the displacement of endothelial cells and formation of lumen within these buds.

• Afterwards, formation of supportive matrix by fibroblasts with increased division around new capillaries plays a role.

• It is the disruption of the balance between apoptosis-inducing and -preventing systems in cells. Apoptosis is the self-destruction of a cell by the stimulation of a genetically programmed series of sequential biochemical events. It should be distinguished from necrosis, which is the irregular disintegration of damaged cells in the body and the formation of an inflammatory reaction by the resulting products. In apoptosis, the cell does not disintegrate, but is destroyed in its own membrane. In addition, since the inflammatory triggering components are not spread around, inflammation is not observed in apoptosis.

1.11.2. Apoptosis; develops by activating two death pathways that result in cell death:

1.11.2.1. Death receptor pathway: Death receptors; are transmembrane receptor proteins in the form of trimers belonging to the tumor necrosis factor receptor family, found in many cell types. These

activate the cytoplasmic enzyme caspase 8 when stimulated by tumor necrosis factors or TRAIL substance outside the cell. The activation of this enzyme stimulates the common effector caspases located in the distal subsection of the pathway.

1.11.2.2. Mitochondrial pathway: DNA damage is activated in the cell. In addition, anti-apoptotic Bcl-2-like proteins, which are cytoplasmic proteins, are activated by their proteins (p53 protein). These release cytochrome c from the mitochondria. This enters the apoptosis complex and activates the caspase 9 enzyme with it. It also activates the common effector caspases and these activated enzymes break down the genomic DNA, causing the structural proteins and enzymes in the cell to break and become inactive, resulting in the destruction of the apoptotic cell. Cells have an antiapoptotic mechanism that ensures the survival of the cell. The activation of the survival receptor, a transmembrane receptor protein located in the cell membrane, by survival factors outside the cell activates the anti-apoptotic Bcl-2 protein in the cytoplasm. It also affects the mitochondria and antagonizes the effects of pro-apoptotic factors on them in the cell. Thus, the mitochondrial pathway leading to apoptosis is suppressed by the survival mechanism. In addition, inhibitors of apoptosis proteins in the cell suppress apoptosis by inhibiting caspases in the apoptosis pathways in the cell. Cells that shrink within their own membranes and lose their vitality without being disintegrated as a result of apoptosis are phagocytosed and destroyed by macrophages. Disruption of the balance between apoptotic and antiapoptotic mechanisms in the cell against apoptosis facilitates tumor development.

1.12. Target points related to cell cycle and death in cancer drug development: The events related to cell cycle and death described above, which affect the proliferation and spreading tendency of the cell, are targeted and cancer drugs are tried to be developed that will prevent these events from cell proliferation, tissue spreading and metastasis.

1.13. The place of antineoplastic chemotherapy in cancer treatment:

This has a place in 4 contexts.

1.13.1. Primary chemotherapy: It is chemotherapy applied for curative purposes in some types of cancer, generally in advanced cancers, in cases where other treatments do not contribute to the life span. Tumors that are given chemotherapy for curative purposes include Hodgkin and non-Hodgkin lymphomas, acute leukemias, metastatic and non-metastatic choriocarcinoma and germ cell tumors, and some childhood tumors. It also relieves symptoms in advanced metastatic cases, improves the quality of life, and is beneficial by extending the time until progression and life span. These tumors include breast, ovarian, non-small cell lung cancer, and nasopharynx cancer.

1.13.2. Adjuvant chemotherapy: Chemotherapy is applied to cases that are not metastatic at diagnosis and whose treatment has been completed locally, assuming that there may be micrometastatic foci. The high proliferation fraction in the foci remaining after local treatment makes the treatment applied during this period more effective. This treatment prolongs disease-free survival in tumors such as colorectal cancer, breast and small cell lung cancer.

1.13.3. Neoadjuvant chemotherapy: In locally advanced cancer, chemotherapy is applied before radiotherapy or surgery to reduce the volume of the tumor, increase the chance of local treatment and in some cases, allow for protective treatments for organs and treat micrometastases early. Neoadjuvant chemotherapy is a preferred treatment approach in stage 3 breast cancer, due to the high probability of the tumor being metastatic at diagnosis. In soft tissue and bone tumors, neoadjuvant chemotherapy may enable limb-sparing surgery. In head and neck tumors, such as laryngeal cancer, neoadjuvant chemotherapy and radiotherapy may prevent organ and function loss.

1.13.4. Concurrent chemo-radiotherapy: Chemotherapy-radiotherapy is applied together to increase the effectiveness of radiotherapy. The selected chemotherapeutic should have radiosensitizing properties. Since the desired effect in concomitant application is to increase radiosensitivity, drugs are applied in low doses. Drugs used for this purpose include cisplatin, 5-fluorouracil and paclitaxel (Bilgiç et al., 2023b).

1.14. Common side effects of antineoplastics:

1.14.1. Myelotoxicity: The most important cause of mortality and morbidity in treatment with antineoplastics is bone marrow toxicity, and this is dose-limiting. It is the decrease in the production of cells responsible for immunity (leukocytes), oxygen carriers (erythrocytes) and cells responsible for normal blood clotting (platelets). Antineoplastics; Except for bleomycin, asparaginase, cisplatin and vincristine, the rest cause myelotoxicity. Anemia is less of a problem

compared to thrombocytopenia and neutropenia. Fever may be observed in neutropenic patients, related to the duration and depth of neutropenia. Thrombocytopenia may develop as a result of bone marrow toxicity. Transfusion may be required due to thrombocytopenia and anemia. Period-specific ones such as vinblastine, methotrexate, pyrimidine and purine antimetabolites may cause early bone marrow suppression. Non-period-specific ones such as busulfan, nitrosoureas and mitomycin generally develop later and long-lasting cumulative toxicity. Drug doses should be reduced when serious toxicity occurs in chemotherapy applications (Akıcı et al., 2012; Anon, 2022a).

1.14.2. Immunosuppression: They can suppress humoral and cellular immunity and cause immunosuppression. This increases the susceptibility to infections and the incidence of opportunistic infections.

1.14.3. Toxicity to rapidly growing cells: Fluorouracil, methotrexate, ara-C, dactinomycin and etoposide are toxic to the digestive system mucosa. This condition, which can affect the entire epithelial surface from the mouth to the anus, is called mucositis. Depending on the location, ulcers, stomatitis, and enteritis-like forms occur in the mouth. Palifermin, a new keratinocyte growth factor drug, can be used in the treatment of severe mucositis in hematological malignancy cases where high doses of drugs are used, such as myeloablative therapy. Antineoplastics such as anthracyclines, cytarabine, and taxanes cause alopecia by destroying the cells that constantly proliferate in hair follicles. Some of the chemotherapeutics

disrupt the rapidly proliferating germ cells in the gonads; They disrupt spermatogenesis in men, oogenesis and sex hormone production in women. As a result, infertility, amenorrhea, early menopause and sometimes impotence can be seen. Therefore, in men (who have a high probability of permanent infertility), sperm can be collected before chemotherapy (alkylating agents) and stored for artificial insemination in the future.

1.14.4. Teratogenic and embryotoxic effects: Antineoplastics create strong teratogenic and embryotoxic effects. Most chemotherapeutics cannot be applied especially in the first trimester of pregnancy. Patients receiving chemotherapy should use effective birth control methods.

1.14.5. Mutagenic and carcinogenic effects: Chemotherapy and radiotherapy have mutagenic and carcinogenic effects. The second of these effects leads to the development of secondary cancer, which is a late complication of treatment. Overly effective treatment approaches prolong the survival of patients, and this situation paves the way for an increase in the frequency of secondary cancers. It is known that the use of antineoplastics in the treatment of cancer or other diseases increases the probability of developing some secondary malignancies (acute myeloid leukemia (AML) compared to those who have never encountered them. Especially alkylating agents, epipodophyllotoxins and anthracyclines are responsible for the development of secondary AML. Total doses and dose intervals of drugs are also important in terms of the development of secondary AML. The use of radiotherapy

together with chemotherapy increases the risk of developing secondary AML even more. In cases where radiotherapy is administered due to cancer, the risk of developing secondary solid tumors in the area where radiation is given also increases. When the preparation processes of these drugs are not carried out under appropriate conditions, they also pose a risk to healthcare personnel. Pregnant women should not enter these areas. Mutagenic effects are a feature of antineoplastic drugs, especially alkylating agents. Chromosomal anomalies have been detected in patients and healthcare personnel exposed to these drugs.

1.14.6. Nausea and vomiting: Most antineoplastics have emetogenic effects to varying degrees. Depending on the type of drug used, dose and method of administration, a spectrum ranging from mild nausea to emesis that can lead to dehydration can be observed. Classic emesis begins within one to two hours after the drug is administered and continues for more than 24 hours. Nausea and vomiting that occur within 24 hours after drug administration is called acute emesis. Nausea and vomiting that occur from the 2nd day following the administration of the drug is called delayed emesis.

1.14.6.1. Ranking of some drugs according to the degree of risk of emetic effect: Bevacizumab, Bleomycin, Busulfan, Fludarabine, 5-Fluorouracil, 6-Mercaptopurine, Methotrexate, Vinblastine, Vincristine, Vinorelbine, strong, moderate and weak emetogenic drugs cause emesis in approximately more than 90%, 30-90% and less than 10% of patients, respectively, when administered intravenously (Iraz et al., 2015). The emetic effect of antineoplastics is

partly due to serotonin released from enterochromaffin cells in the gastrointestinal mucosa, stimulating serotonin 5-HT3 receptors in the abdominal vagal afferent nerve endings, indirectly triggering the vomiting center in the brainstem. This effect is prevented by 5-HT3 receptor blockers or by bilateral abdominal vagotomy and cutting the splanchnic nerves. Direct stimulation of the "chemoreceptor trigger zone" (CTZ) in the brain by drugs or their metabolites also contributes to emesis. CTZ transmits the stimuli to the vomiting center. Personal factors also play a role in sensitivity to the emetic effect of the drug. The most sensitive are women, those under 50 years of age, those with a history of motion sickness, and anxious patients. Neuroleptics such as phenothiazines, butyrophenones, and metoclopramide are used in the prevention and treatment of vomiting and nausea caused by antineoplastics. In those under 20 years of age, domperidone is used instead of metoclopramide because its extrapyramidal side effects are increased. The use of antiemetics with glucocorticoids increases antiemetic efficacy. If the above drugs are insufficient, dexamethasone or lorazepam is added to them. In cases with high risk of emesis or if the above drugs are insufficient, oral 5-HT3 receptor blocker strong antiemetics (such as ondansetron, granisetron, dolasetron, granisetron and palanosetron) are used and if necessary oral dexamethasone is added. In combination with cyclophosphamide and adriamycin, which have strong emetogenic effects, aprepitant, a neurokinin receptor antagonist, is given orally in cisplatin-based chemotherapy. In refractory vomiting that does not respond to routinely used drugs, the active substance of cannabis, delta-9-tetrahydrocannabinol, is used.

Oral dexamethasone is preferred to prevent delayed emesis, alone or in combination with metoclopramide (domperidone under the age of 20) or prochlorperazine. 5-HT3 receptor blockers are not as effective in delayed emesis as in acute emesis. To prevent anticipatory emesis, an amnesic (memory suppressant), sedative and anxiolytic drug, lorazepam or a similar anxiolytic is used.

1.14.7. Local reaction: Most antineoplastics are administered intravenously. Extravasation of some antineoplastics causes pain, erythema, induration, necrosis and deep ulcers. Anthracyclines and vinca alkaloids are among the drugs that can cause such reactions (Yarsan & Aktaş 2012; Yarsan & Aktaş 2017).

1.14.8. Tumor lysis syndrome and hyperuricemia: In tumor cases with a high proliferative index, if the tumor is highly sensitive to the drug, a large number of tumor cells are destroyed in a short time and hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia develop due to this. These disorders can lead to kidney damage, cardiac arrhythmia and convulsions. This clinical picture is called tumor lysis syndrome. The reason for these events is the excessive cell destruction due to chemotherapy and the increased production of uric acid from purine bases formed as a result of nuclear fragmentation and the release of potassium and phosphates in the destroyed cells. In such cases, ensuring the patient's hydration and oral administration of allopurinol, a xanthine oxidase inhibitor, 24 hours before treatment reduces the possibility of acute urate nephropathy. Hyperuricemia is especially evident in the treatment of high-grade lymphoma and leukemia. In

addition to allopurinol, urate breakdown can be accelerated with rasburicase, a recombinant urate oxidase preparation.

1.14.9. Allergic reactions: Allergic reactions can be observed with some antineoplastics. Urticaria, pyretic reactions, angioedema and even anaphylaxis may occur. For example, bleomycin can cause pyretic, taxanes can cause anaphylaxis and etoposide can cause hypotensive reactions.

1.14.10. Other toxic effects: Chemotherapeutics also have specific organ toxicities. Cisplatin for nephrotoxicity. Doxorubicin for cardiac toxicity.

2. ANTINEOPLASTIC DRUGS

Antineoplastic drugs are applied in the clinic by medical oncology specialists.

2.1. Cytotoxic Drugs

They are divided into ten subclasses explained below.

2.1.1. Alkylators Affects the S and G1 periods of the cell cycle.

Mechanism of action: They are prodrugs. In most cancer cells, they turn into ethyleneimonium species that are suitable for them and then into carbonium species that contain positively charged carbon. Carbonium ion is a reactive metabolite with strong electrophilic properties. Alkylation occurs by irreversibly binding to nucleophilic groups such as thiol, phosphate, amino, imidazole, carboxyl and

hydroxyl groups in the content of negatively charged nucleic acids, especially DNA and other macromolecules, with covalent bonds. Antineoplastic effect occurs by covalent binding of the active metabolite to DNA. Monofunctional drugs bind to DNA at one point. However, the majority of alkylating cancer drugs are bifunctional. They bind to double-stranded DNA at two points. If the two points are on one of the strands of the double helix, there is cross-linking between the strands, and if they are on the same strand, there is intra-strand binding. If one of the points to which the active or reactive metabolite binds is on DNA and the other is on histone, there is DNA protein binding. Alkylation disrupts the transcription and replication of DNA. The place where reactive metabolites consisting of carbonium ions or alkylators in therapeutic concentrations frequently bind to the DNA molecule is the 7th nitrogen atom of guanine. Alkylation of this place causes one of three changes in the DNA molecule:

1. Alkylation of guanine from the 7th nitrogen increases the acidity of the number 1 nitrogen atom of this substance. The developing change in the molecule encourages it to form a base pair with thymine instead of cytosine. The development of an abnormal base pair with the binding of alkylators causes the genetic code to be read incorrectly, that is, adenine undergoes a similar process to guanine during transcription and replication. This situation causes disorder in the new DNA strand and mRNA molecule.

2. The imidazole ring of guanine opens and guanine is broken and eliminated. As a result, the DNA chain is broken from there.

3. The developing reactive metabolite forms a bridge between guanine in two different chains. In this case, transcription and replication of DNA do not occur. These drugs also alkylate enzymes and proteins, disrupting intermediary metabolism and respiration in the cell. The structural disorders they create in the cell are similar to those in cells exposed to radioactive rays, so alkylating drugs are also called radiomimetic drugs. The types of tumors that are most sensitive to X-rays are equally sensitive to these drugs. They should not be given with radiotherapy; they increase the toxicity caused by the rays in the tissue. Some of the antineoplastics (such as anthracycline derivatives and mitoxantrone, which are structurally similar to them) also intercalate in the DNA molecule. Intercalation should not be confused with the cross-linking that occurs as a result of bifunctional alkylation and is explained above. Intercalation occurs with drugs or metabolites whose molecules are planar. Molecules with this structure enter the grooves between two adjacent base pairs in the DNA double helix and superimpose reversibly on the DNA strands. Reversible binding can turn into irreversible binding over time. Intercalation at many points on the same DNA double strand causes neighboring base pairs to move away from each other, elongating the chain and decreasing its helicity. As a result, DNA replication and transcription are disrupted. However, alkylating drugs do not intercalate. Resistance Resistance to alkylating drugs is a very common situation during treatment. Except for nitrosoureas and triazene derivatives, a tumor that becomes resistant to one alkylating agent also becomes resistant to others. This situation is called cross-resistance. Resistance formation in the cell is a change in the

permeability to the drug or an increase in the amount of nucleophilic-thiol groups that hold the drug in components of the cell other than DNA. Unlike antimetabolites, resistance to alkylators develops slowly and is associated with multi-stage mutation (Aktaş & Bayram, 2020b). Common pharmacological properties

Side effects and pharmacological properties:

• They suppress bone marrow and lymphoid tissue. Since the effect of doses in the bone marrow lasts long, it is reflected in blood cells late. The duration of this effect is the most important criterion in determining the interval between doses. Their disruption of lymphoid tissue also forms the basis of their immunosuppressive activity. These effects reduce the number of leukocytes, lymphocytes and platelets in the blood. Since erythrocytes have a long life and a slow speed, there is no significant decrease in their numbers. The duration of reaching the maximum and continuing of these effects varies between drugs. The shortest effect is cyclophosphamide with 3 weeks. The effects of mechlorethamine and nitrosoureas are 6 weeks. Bone marrow is most sensitive to busulfan, ethyleneimines and nitrosoureas. Lymphocytes are sensitive to bichlorethylamines, especially cyclophosphamide. The most toxic of these to the bone marrow is busulfan. Lymphocytes are not affected much by busulfan, ethylenimines and nitrosoureas. Therefore, these drugs do not have immunosuppressive activity. Busulfan is the one that causes thrombocytopenia the most among alkylating agents. Therefore, blood counts should be done at certain intervals during their application and should be discontinued when

there is a tendency towards thrombocytopenia and leukopenia. Cumulative bone marrow toxicity is also observed in most of these drugs.

• Bichloroethylamine derivatives and nitrosoureas cause vomiting, nausea and loss of appetite. These side effects become more pronounced with IV application.

• They develop ulcers and inflammation in the oral and intestinal mucosa,

• They have carcinogenic, mutagenic and teratogenic effects. They also have toxic effects on the gonads.

• They can cause hair loss by destroying hair follicle cells (cyclosphamide more often).

Alkylators are divided into four subgroups according to their chemical structure:

They covalently bind to many points in the cell's DNA double strand and alkylate DNA molecules. They disrupt intermediary metabolism and respiration in the cell by alkylating enzymes and proteins and lead to inhibition of cancer cells. They are period-specific drugs (Dökmeci & Dökmeci, 2016).

2.1.1.1. Nitrogen mustards (bichloroethylamines): Used in cancer treatment for many years; chlormethine, melphalan and chlorambucil are the main nitrogen mustard compounds. It is used in combination with prednisone, vinca alkaloids and procarbazine in

breast, ovarian and Hodgkin's type cancers (Dökmeci & Dökmeci, 2016).

2.1.1.1.1. Cyclophosphamide: Interferes with DNA replication and RNA formation. It is successful in solid and hematological tumors. It is used in combination with other antineoplastics in many types of neoplastic diseases (such as some types of leukemia, lymphomas and solid tumors). It has a strong immunosuppressive effect. Due to this feature; it is also used in the treatment of autoimmune disorders such as Behcet's disease, rheumatoid arthritis and nephrotic syndrome. Side effects: Digestive system disorders such as nausea and vomiting and bone marrow suppression. Depending on the bone marrow; thrombocytopenia and leukopenia decrease to the lowest level 1-2 weeks after the application of the drug. Its specific effects are sterile hemorrhagic cystitis and urothelial toxicity. This condition is due to its metabolite, acrolein, which is excreted in urine. Developing cystitis can turn into fibrosis in the bladder and cause bladder cancer (Akıcı et al., 2012; Anonymous, 2022b).

2.1.1.1.2. Mechlorethamine: Prevents cell proliferation by binding to DNA and cross-linking the two strands. It binds to the N7 nitrogen on the guanine base of the DNA. Its spectrum of action includes lymphoid malignancies such as Hodgkin's disease, lymphosarcoma, chronic myelocytic leukemia, polycythemia vera and bronchogenic carcinoma. It is often administered intravenously. However, when combined with a topical formulation, it can also be used to treat skin diseases. Topical application is effective in mycosis

fungoides type cutaneous T-cell lymphoma (Akıcı et al., 2012; Anonymous, 2022c)

2.1.1.1.3. Chlorambucil: It acts by blocking DNA and RNA formation. It is used to treat chronic lymphocytic leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma, Waldenström macroglobulinemia, polycythemia vera, trophoblastic neoplasms, and some types of ovarian carcinoma. It has also been used as an immunosuppressive drug for various autoimmune and inflammatory conditions such as nephrotic syndrome. Bone marrow suppression (anemia, neutropenia, and thrombocytopenia) is the most common reversible side effect (Anonymous, 2022d).

2.1.1.1.4. Melphalan: It chemically alters the DNA nucleotide guanine through alkylation. It causes connections between DNA strands. This chemical change prevents DNA and RNA synthesis, which is necessary for cell survival. These changes cause cytotoxicity in dividing and non-dividing tumor cells. It is used in the treatment of multiple myeloma, ovarian cancer, melanoma and AL amyloidosis. It is especially included in the preparation regimens in autologous stem cell transplantation. It can also be used for regional perfusion into the extremity artery in malignant melanoma and soft tissue sarcoma of the extremities. As a side effect; It can cause interstitial pneumonia and fibrosis in the lung. It also causes nausea and bone marrow suppression (Akıcı et al., 2012; Anonymous, 2022e).

2.1.1.1.5. Ifosfamide: It acts by disrupting the copying of DNA and the formation of RNA. It is applied in soft tissue sarcoma,

osteosarcoma, testicular, bladder, small cell lung, cervical and ovarian cancers. Side effects; Hair loss, vomiting, blood in the urine, kidney problems, bone marrow suppression and decreased level of consciousness are observed (Anonymous, 2020a).

2.1.1.2. Ethyleneimines and methylmelamines

2.1.1.2.1.Thiotepa: Used in combination with HPCT-supported high-dose chemotherapy in the treatment of Hodgkin's disease, leukemia, solid tumors. It is also used prophylactically to prevent seeding of tumor cells in breast and ovarian adenocarcinoma, papillary thyroid, cystoscopic biopsy. It is also used as an adjuvant agent in biopsy and as a therapeutic agent in preventing recurrence after cystoscopic resection of bladder tumors. The effectiveness in tumor control can reach 55%. Its side effect is bone marrow suppression resulting in leukopenia, thrombocytopenia, and anemia (Anonymous, 2022f).

2.1.1.2.2.Altretamine: It acts by formaldehyde-mediated DNA-protein interchain cross-linking, which is an iminium intermediate (Anonymous, 2022g). It is used in lung tumors, breast cancers and small cell lung cancers. In addition, it is a drug used for the treatment of advanced ovarian and cancer. It can cause peripheral and central neuropathy, kidney and liver toxicity and hematological disorders (Akıcı et al., 2021; Dökmeci & Dökmeci, 2016).

2.1.1.3. Alkyl sulfonates

2.1.1.3.1. Busulfan: It is used in combination with cyclophosphamide or fludarabine / clofarabine as a conditioning agent before bone marrow transplantation in leukemias, lymphomas and myeloproliferative disorders. It is especially applied together with cyclophosphamide in the preparation procedures of cases where allogeneic hematopoietic stem cell transplantation will be applied. Rare side effects that develop in long-term application are pneumonitis accompanied by persistent cough and progressive dyspnea. Its bone marrow suppressive effect is strong. Hyperpigmentation occurs frequently (Akıcı et al., 2012; Anonymous, 2021a).

2.1.1.3.2. Treosulfan: It is converted into compounds called epoxide (a substance that kills rapidly growing cells by binding to their DNA while they are dividing). Together with fludarabine; It is indicated for conditioning treatment before allogeneic hematopoietic stem cell transplantation. Side effects; It causes skin pigmentation, lung disorder and hemorrhagic cystitis (Anonymous, 2022h).

2.1.1.4. Nitrosoureas: Carmustine, semustine and lomustine are in this group. Chloroethyl derivative nitrosoureas are unstable compounds and spontaneously transform into alkylating and carbamoylating intermediates under physiological conditions.

They interact with macromolecules in the nucleus in the following ways:

1. Monofunctional alkylation of DNA and proteins,

2. Bifunctional alkylation by bridging (cross-linking) between DNA strands,

3. Cross-linking between DNA strands and proteins,

4. Breaking DNA strands,

5. Carbamoylating proteins.

Nitrosoureas are lipophilic compounds. They are well absorbed in the gastrointestinal tract and cross the blood-brain barrier. They are effective in malignant tumors of the CNS. They suppress bone marrow more than other alkylating drugs. Drug-induced leukopenia reaches low levels in 4-6 weeks and thrombocytopenia in 3-5 weeks. This condition usually normalizes in 1-2 weeks. Like most other alkylating drugs, they have teratogenic, mutagenic and carcinogenic effects. They are also nephrotoxic.

2.1.1.4.1. Carmustine: They act by creating cross-links between chains that prevent DNA replication and DNA transcription. It is used to treat glioma, glioblastoma multiforme, medulloblastoma, astrocytoma, multiple myeloma, lymphoma and various types of brain cancer. Cumulative kidney damage, hepatotoxicity and late-onset lung fibrosis may develop (Anonymous, 2022ı).

2.1.1.4.2. Lomustine: Alkylates DNA and RNA. It creates cross-links between chains in DNA. It can also inhibit several important enzymatic processes through carbamoylating amino acids in proteins. It is a highly lipid-soluble drug. Therefore, it crosses the blood-brain barrier. This feature is used in the treatment of brain tumors, which is

its primary use. However, it is also used in the treatment of Hodgkin lymphoma as a secondary option. It can cause neurotoxicity and emesis (Anonymous, 2022i).

2.1.1.4.3. Estramustine: It is the chemical combination of an estrogen and chlormethine, which is an alkylating drug. For this reason, it creates a hormonal effect of reducing testosterone levels and an alkylating antimitotic effect. It is mainly used in the treatment of prostate cancer (Akıcı et al., 2012).

2.2. Anthracycline and Cytotoxic Antibiotics: They are antineoplastics with antibiotic properties due to being obtained from the culture of different microorganisms. Anthracycline derivatives; daunorubicin, epirubicin, doxorubicin, aclarubicin, idarubicin and other cytotoxic antibiotics mitomycin, bleomycin, dactinomycin and mitoxantrone are also in this group. They should not be administered simultaneously with radiotherapy because they show radiomimetic activity. They increase the toxicity caused by radiation in the tissue. They show period-specific effects

2.2.1. Anthracycline derivatives: There are 5 drugs in this group. Doxorubicin and daunarubicin are natural anthracyclines obtained from a fungus called Streptomyces peucetius. Idarubicin and epirubicin are semi-synthetic derivatives of these. Anthracyclines form free radicals with high cytotoxic activity in tissues. In addition, they react with oxygen in the tissue and develop cytotoxic free oxygen radicals. This plays a role in destroying malignant cells and in their toxic effects on organs, especially the heart. In the myocardium, it

causes irreversible cardiomyopathy and congestive heart failure in proportion to the total cumulative doses applied.

2.2.1.1. Doxorubicin: They act by intercalating between the DNA double strand and disrupting DNA synthesis (Bilgic et al., 2020). It is included in combinations (bleomycin, vinblastine, prednisone and dacarbazine) as the first-line drug in acute leukemia, non-Hodgkin lymphomas, breast, testicular, ovarian and bronchial cancers (Aktaş Sevimli, & 2020c; Tutun et al., 2019).

2.2.1.2. Pegylated doxorubicin: IV administration of liposomal docorubicin preparations prepared by encapsulating in liposomes produces less cardiotoxic effect than the standard preparation. It also causes less tissue necrosis when exuded. It may cause "hand-foot syndrome", which manifests itself with painful red spots on the hands and feet, more frequently with the liposomal preparation. It is treated by cooling the hands and feet and removing socks and similar clothing if any (Akıcı et al., 2012).

2.2.1.3. Liposomal doxorubicin: It is doxorubicin encapsulated in liposomes. Its activity is similar to doxorubicin. It is less cardiotoxic. It is used in the treatment of Kaposi's sarcoma (lesion that develops in this AIDS-related disease, growth in the throat, mouth, skin, nose and other organs) and treatment-resistant ovarian cancer.

2.2.1.4. Daunorubicin: Produced from Streptomyces peucetius. Used in the treatment of acute myeloid and acute lymphocytic leukemia. Used in the treatment of AIDS-related Kaposi's sarcoma (Anonymous, 2022k).

2.2.1.5. Epirubicin: Forms a complex with DNA by inserting its planar rings between nucleotide base pairs. This prevents replication and transcription. It also triggers DNA cleavage by topoisomerase II. It then stabilizes the topoisomerase II-DNA complex, causing irreversible DNA strand breakage that leads to cell death. In addition, it can produce cytotoxic free radicals that are very reactive against DNA, cell membranes, and mitochondria. It is used in the treatment of breast and bladder cancer (administered into the bladder). Side effects are alopecia, nausea/vomiting, cardiotoxicity, leukopenia, and stomatitis (Anonymous, 2022l).

2.2.1.6. Idarubicin: It enters DNA and interferes with the topoisomerase II enzyme, preventing DNA from unraveling. It is combined with cytosine and arabinoside as the first-line treatment of acute myeloid leukemia. It is used in the treatment of acute lymphoblastic leukemia and chronic myeloid leukemia in blast crisis (Anonymous, 2022m).

2.2.1.7. Aclarubicin: It is obtained from Streptomyces galilaeus aclarubicin. It is applied in acute myeloid leukemia resistant to primary chemotherapy or not responding at all

2.2.2. Cytotoxic antibiotics

2.2.2.1. Bleomycin sulfate: It is an antibiotic obtained from Streptomyces verticillus culture. It acts by creating free radicals in the cell and inducing breaks in the DNA chain. They should not be used with radiotherapy. They show period-specific activity. It is applied in

combination with cisplatin in testicular carcinomas, head, neck, cervix, skin ovarian cancer and Hodgkin and less commonly non-Hodgkin cancers. Bone marrow suppression is mild. Its important side effect is pneumonitis and fibrosis in the lung. Lung complications are observed in approximately 10% of those treated and result in death in the elderly with insufficient lungs. Patients treated with the drug should be monitored with respiratory tests, especially carbon monoxide diffusion and radiology tests. It causes skin thickening, hyperpigmentation, hyperkeratosis-like skin lesions on the palms and elbows. It can cause nausea, vomiting, alopecia and allergic reactions (such as fever, chills-tremors, skin rashes and anaphylaxis) (Akıcı et al., 2012).

2.2.2.2. Dactinomycin: It is obtained from Streptomyces parvullus. It forms intercalation by placing transversely between adjacent guanosine-cytosine base pairs in the DNA double-helix. In this way, it disrupts DNA and mRNA synthesis. It is not specific to the period. It is indicated for rhabdomyosarcoma, Wilms tumor, trophoblastic neoplasm, Ewing sarcoma, testicular and ovarian cancer. It suppresses bone marrow. It causes nausea and vomiting, diarrhea, skin rashes, hyperpigmentation, ulcers in the mouth and intestines. It is irritating. It has a teratogenic effect (Akıcı et al., 2012).

2.2.2.3. Mitoxantrone: Cross-links to the DNA double strand. Kills cells that reproduce and complete their reproduction. It is not specific to the period. It is used in the treatment of metastatic breast cancer. It is also used in the treatment of acute non-lymphocytic leukemia, non-Hodgkin lymphoma and primary hepatocellular

carcinoma that are not amenable to resection. It increases the survival rate of children in acute lymphoblastic leukemia relapse. Prednisone combination is the second-line treatment for metastatic hormone-resistant prostate cancer. Side effects; suppresses bone marrow. It has a toxic effect on the myocardium. It also causes nausea, vomiting, stomatitis and alopecia (Anonymous, 2022n).

2.2.2.4. Mitomycin: It is a natural product containing aziridine isolated from Streptomyces caespitosus and Streptomyces lavendulae. It prevents its synthesis by cross-linking and alkylating DNA. It is period-specific. It is used locally (by instillation) in breast, pancreatic, gastrointestinal (such as stomach and esophagus) and bladder cancer. Its side effects are microangiopathic hemolytic anemia and bone marrow suppression (Anonymous, 2022p).

3. ANTIMETABOLITES

They are analogs of different metabolites that act as substrates or coenzymes in various stages of the production chain of RNA, DNA, and proteins, which are the basic elements of the cell. They compete with these natural substrate-using enzymes for binding sites and prevent the enzyme from binding and preventing the enzyme from working. They are period-specific and are often applied in tumors with a high proliferation tendency. Their toxic effect is on the intestinal mucosa and bone marrow.

3.1. Methotrexate: It competitively inhibits dihydrofolate reductase (DHFR), the enzyme that enters the production of

tetrahydrofolate. Its affinity for DHFR is approximately 1000 times that of folate. DHFR catalyzes the conversion of dihydrofolate to active tetrahydrofolate. Folic acid is required for the de novo production of nucleoside - thymidine. In addition, it is also required for DNA synthesis. In addition, it is also necessary for purine, pyrimidine and folate base biosynthesis and therefore inhibits synthesis. They inhibit the synthesis of DNA, RNA, thymidylates and proteins. The decrease in the affinity of dihydrofolate reductase enzyme to methotrexate as a result of mutation in the tumor cell plays a role in the development of resistance. It is applied in the treatment of breast, head, neck, leukemia, lymphoma, lung, osteosarcoma, bladder and trophoblastic neoplasm type cancers. Side effects; nausea, fatigue, fever, increased risk of infection, low white blood cell count and disintegration of the skin in the mouth (Akıcı et al., 2012; Anonymous, 2022r).

3.2. Raltitrexed: It inhibits thymidylate synthase and prevents the formation of precursor pyrimidine nucleotides, thus preventing DNA and RNA formation.

Its effect; It is applied in advanced colon, breast and ovarian cancer and malignant pleural mesothelioma-like tumors. Side effects include loss of appetite, weakness, significant gastrointestinal disorders such as diarrhea, and myelosuppression (Anonymous, 2022s).

3.3. Pemetrexed: It affects the formation of DNA and RNA (by preventing the formation of precursor purine and pyrimidine nucleotides) that are necessary for the growth and survival of normal and cancer cells. Side effects include low blood cell counts measured

by complete blood count, gastrointestinal disorders, myelosuppression and skin rash. Oral folic acid and parenteral vitamin B12 administration reduce its side effects. It is used with cisplatin in malignant pleural mesothelioma and lung adenocarcinoma (Anonymous, 2022t).

3.4. Purine antimetabolites: This group includes mercaptopurine, thioguanine, fludarabine and cladribine.

3.4.1. Mercaptopurine: They show cytotoxic effects by disrupting DNA and RNA synthesis. They are also applied in autoimmune disorders and cancer. It is also used in the treatment of acute lymphocytic and chronic myeloid leukemia, Crohn's disease and ulcerative colitis. It is also used with methotrexate in acute lymphocytic leukemia. Its side effects are vomiting, bone marrow suppression, liver toxicity and loss of appetite (Anonymous, 2022u).

3.4.2. Tioguanine: In the cell, it is converted to its metabolite 6-tioguanine5'-phosphate. The intermediate metabolite disrupts vital pathways. It also participates in the structure of DNA and RNA and has a cytotoxic effect. It treats acute lymphocytic leukemia and chronic myeloid leukemia. It is added as the third drug to the anthracycline and cytarabine combination used for remission induction in acute myelocytic leukemia. Its side effects are leukopenia and neutropenia, thrombocytopenia, anemia, liver problems and mouth inflammation (Anonymous, 2022u).

3.4.3. Fludarabine: Prevents DNA synthesis by interfering with ribonucleotide reductase and DNA polymerase. It is active against dividing and resting cells. It is indicated for acute lymphocytic, chronic

lymphocytic leukemia, acute myeloid leukemia and non-Hodgkin lymphoma. Side effects are brain dysfunction, low blood cell count and lung inflammation. It also suppresses cellular immunity and paves the way for opportunistic infections (Anonymous, 2022v).

3.4.4. Cladribine: It acts by inducing apoptosis in non-dividing cells. It creates complete remission in hairy cell leukemia. Its myelotoxic effect is strong. It causes cellular type immunodeficiency. It increases the incidence of opportunistic infections and causes acute renal failure (Akıcı et al., 2012).

3.3. Pyrimidine antimetabolites: This group includes; 5-fluorouracil, capecitabine, tegafur with uracil, nelarabine, gemcitabine, cytarabine and clofarabine.

3.3.1. Fluorouracil: It shows cytotoxic effect by blocking thymidylate synthase action and stopping DNA production. It is applied in colorectal, esophageal, stomach, pancreas, breast and cervical cancer. It is applied as a cream in actinic keratosis, basal cell carcinoma and skin warts. Side effects; mouth inflammation, loss of appetite, low blood cell count, hair loss and skin inflammation are observed (Anonymous, 2022y).

3.3.2. Cytarabine: It shows effect by blocking the function of DNA polymerase. It is applied in acute and chronic myeloid leukemia, acute lymphocytic leukemia and non-Hodgkin's lymphoma cancers. Side effects; bone marrow suppression, vomiting, diarrhea, liver problems, rash, mouth ulcer formation and bleeding (Anonymous, 2022z).

3.3.3. Clofarabine: It is applied by i.v. infusion in cases of acute lymphoblastic leukemia. Side effects; It can cause cardiovascular disorder, neuropathy, cough, shortness of breath, itching, skin rash and sweating.

3.3.4. Nelarabine: It is used in the treatment of T-cell acute lymphoblastic leukemia and refractory T-cell lymphoblastic lymphoma. It creates neurotoxic side effects.

3.3.5. Uracilli / Tegafur: Excess uracil competes with 5-FU for DPD. Thus, it inhibits 5-FU catabolism. It is taken up by cancer cells. It is broken down into 5-FU, a substance that kills tumor cells. Uracil kills cells by allowing higher amounts of 5-FU to remain inside them. It is used in bowel cancer (Anonymous, 2022aa).

3.3.6. Capecitabine: It gains effectiveness by converting to fluorouracil in the body. Thymidine and uridine phosphorylase activity, which are necessary for the formation of the active metabolite, is higher in tumor tissue than in healthy tissue. Therefore, drug activation in the tumor occurs at higher levels compared to healthy tissue. It treats breast (with docetaxel), stomach, esophagus and colorectal cancer. Side effects are blood clotting problems, allergic reactions, cardiomyopathy and low blood cell count (Akıcı et al., 2012; Anonymous, 2022ab).

3.3.7. Gemcitabine: Blocks new DNA formation resulting in cell death. It acts against neoplastic growth. It inhibits the replication of Orthohepevirus A, the causative agent of the disease. It is used alone as a first-line treatment for pancreatic cancer and in combination with cisplatin for metastatic bladder and non-small cell lung cancer. It is used

in combination with carboplatin for ovarian cancer. It is used as a second-line treatment in combination with paclitaxel for metastatic breast cancer that cannot be surgically removed. Side effects include bone marrow suppression, liver and kidney problems, nausea, fever, rash, shortness of breath, mouth sores, diarrhea, neuropathy, and hair loss (Anonymous, 2022ac).

4. VINCA ALKALOIDS AND ETOPOSIDE

The dimeric alkaloids of Vinca rosea are vinblastine, vincristine and their semi-synthetics vinorelbine and vindesine. Etoposide is the semi-synthetic of podophyllotoxin obtained from Podophyllum. The primary effect of these, except for etoposide, is to prevent the development of mitotic spindles consisting of microtubules in the metaphase stage of mitosis. They bind to tubulin molecules, which are the structure of microtubules, and prevent them from coming together to form microtubules. As a result, cell division stops in the metaphase stage and the cell dies. They are mitosis-specific preparations. Since they disrupt the formation of neuron microtubules without disrupting DNA formation and structure, they also have a neurotoxic effect. They have vesicant and teratogenic effects.

4.1. Vinblastine sulfate: Used in the treatment of tumors such as testicular cancer and lymphoma. It is also effective in choriocarcinoma, breast cancer, head and neck cancer, neuroblastoma, mycosis 1ungoides and histiocytosis X. The most common side effects are leukopenia, nausea and vomiting and alopecia. Peripheral and central neuropathy are less common than vincristine.

4.2. Vincristine sulfate: Used in the treatment of neuroblastoma, lymphoma, Ewing sarcoma, small-cell lung, embryonal rhabdomyosarcoma, acute lymphoblastic and chronic lymphocytic leukemia, cervix and breast and multiple myeloma cancer. Its dose-limiting effect is autonomic and peripheral neuropathy. Alopecia, nausea and vomiting may occur. Since it is a vesicant, it causes serious cellulitis and necrosis if it leaks out of the vessel and may lead to phlebitis.

4.3. Vindesine sulfate: Treats breast cancer, acute lymphoblastic leukemia, malignant melanoma, Hodgkin's disease, small cell lung and non-Hodgkin's lymphoma. It is similar to vinblastine in terms of side effects.

4.4. Vinorelbine: It acts by inhibiting mitosis by interacting with tubulin. It is used in metastatic breast and non-small cell lung cancer and rhabdomyosarcoma. It has a significant myelotoxic effect (Anonymous, 2022ad).

4.5. Etoposide: It causes DNA damage by stopping the cell cycle in the late S or G2 period. It is used in Kaposi's sarcoma, Ewing's sarcoma, lung and testicular cancer, lymphoma, non-lymphocytic leukemia and glioblastoma multiforme-like cancer. It is also used together with bleomycin in the treatment of testicular cancer. It is also used in a conditioning regimen before bone marrow and blood stem cell transplantation. As a side effect; There are bone marrow suppression, lymphoid hypoplasia, nausea, vomiting, alopecia, fever, peripheral

neuropathy, phlebitis, mucositis and cardiotoxicity (Anonymous, 2022 ae).

5. PLATINUM COMPOUNDS

They are organic platinum type drugs. Cisplatin, which was the first treatment, is chemically platinum diamminodichloride. During experiments conducted to investigate the effect of the electrical field created by platinum electrodes in liquid medium on the growth of E. coli, cisplatin was discovered when the antibacterial and antineoplastic effect of the platinum type passing from the electrode to the liquid was noticed.

5.1. Cisplatin: It creates intra-strand and inter-strand cross-linking in the DNA double-strand. Its mode of action is similar to that of bifunctional alkylating drugs. Only the cis isomer is cytotoxic. It is not specific to the period.

Indications: Metastatic ovarian and testicular tumors that have undergone radiotherapy or surgical intervention. The combined treatment is cyclophosphamide and cisplatin. Cisplatin is also applied to metastatic ovarian tumors that have not received cisplatin treatment before and are resistant to standard chemotherapy. It finds application in transitional cell bladder cancer that does not respond to local treatments such as radiotherapy or surgery. Since its myelosuppressive effect is moderate, it is a drug suitable for combined treatment. Side effect; acute renal failure, which is dose-dependent (Anonymous, 2022af).

5.2. Carboplatin: It shows its effect by interfering with the copying of DNA. Its spectrum of action is ovarian, lung, head, neck, brain cancer and neuroblastoma. It can be used for some testicular cancers, but cisplatin is more effective. Nausea and vomiting are less severe and easier to control. Its disadvantage is its myelosuppressive effect. This situation reduces the production of blood cells and platelets in the bone marrow to 10% of normal (Anonymous, 2022ag).

5.3. Oxaliplatin: It is a cisplatin analog with reduced toxicity. It creates inter-chain and intra-chain cross-links in DNA, which prevents DNA replication and transcription, causing cell death. In the treatment of colorectal cancer; it is used together with folinic acid, fluorouracil and capecitabine. Its myelosuppressive and nephrotoxic effects are weaker compared to the other two platinum preparations. Its side effect is peripheral sensory neuropathy (Anonymous, 2022ah).

6. TAXANES

It is obtained from *Taxus brevifolia* and is a taxane type diterpene ester. The first preparation found was paclitaxel (Gür and Bilgiç, 2023). Taxanes bind to oligomeric or polymeric substrates, which are the building blocks of tubulin production in the tumor cell, and accelerate tubulin polymerization, thus increasing tubulin formation. As a result, microtubule synthesis in the cell increases. Additional microtubules bind to existing normal microtubules and stabilize them. As a result, the tubulin-microtubule ratio is disrupted and a cytotoxic effect occurs (Gur et al., 2021; Aktaş et al., 2024b).

6.1. Paclitaxel: It works by interfering with the normal function of microtubules in cell division. It is applied in the treatment of ovarian (first and second-line treatment), esophageal, breast, lung, Kaposi's sarcoma, cervical and pancreatic cancer. Side effect; hair loss, bone marrow suppression, numbness, allergic reactions, muscle pain, diarrhea, heart problems, increased risk of infection and lung inflammation (Anonymous, 2022ak; Bilgiç &Aktas, 2022; Gür at al., 2022).

6.2.Docetaxel: It acts by disrupting the normal function of microtubules and stopping cell division. Usage; breast, head and neck, stomach, prostate and non-small cell lung cancer. Also; It treats locally advanced and metastatic breast and small cell breast cancer resistant to antineoplastics

Usage

• Prostate cancer that does not respond to hormone therapy,

• Combined with antineoplastics; head and neck, stomach and adenocarcinoma cancer.

• In adjuvant treatment after surgery in lymph node-positive breast cancer that can be removed with surgical application.

Side effect; low blood cell count (cytopenia), hair loss, shortness of breath, drowsiness, vomiting, nausea, muscle pain and allergic reactions (Anonymous, 2022aı).

6.3. Cabazitaxel: Increases microtubule stabilization and prevents cellular mitosis. It also binds to cellular microtubules and microtubule-associated motor protein, preventing androgen receptor (AR) signaling, thus preventing AR nuclear translocation. It is administered with prednisolone in prostate cancer that has been previously treated with docetaxel and does not respond to hormonal therapy. Premedication with an antihistamine and a corticosteroid should be performed before treatment. Side effect; neutropenia (including febrile neutropenia) is observed (Akıcı et al., 2012; Anonymous, 2022ai).

7. PROTEIN KINASE INHIBITORS

The stimulatory effect of different growth elements on their own receptors is important for the continuation of the cell cycle and cell reproduction. Tyrosine kinase enzymes control the proliferation and growth functions in cancer cells and grow the cancer. Stopping these enzymes makes cancer cells lose their functions. Tyrosine kinases are enzymes that create protein phosphorylation. They take a phosphate group from ATP to tyrosine residues in proteins. They control functions such as apoptosis, cell reproduction and signal transmission. Changes here are important in the development of cancer. It is the inhibition of angiogenesis (new blood vessel formation) in tumor tissue. This situation causes the tumor cells to die because the tumor tissue cannot receive the oxygen and nutrients it needs to sustain its life. Due to this relationship, the antiangiogenic effect of certain drugs turns into an antineoplastic effect. The first TKI agent used was imatinib mesylate,

which is used in gastrointestinal stromal tumors and chronic myeloid leukemia. In the treatment of kidney cancer; small molecule tyrosine kinase inhibitors that block vascular endothelial growth factor receptors (pazopanib, axitinib, sunitinib and sorafenib). The only tyrosine kinase inhibitor used in the treatment of metastatic colon cancer is regorafenib (Akıcı et al., 2012; Benekli, 2020).

Mechanism of action and application: The mechanisms by which protein kinase inhibitor drugs kill cancer cells are explained in the context of imatinib. Imatinib is used in the adjuvant treatment and advanced stages of the disease by strongly and specifically inhibiting this receptor kinase. Imatinib is used in the treatment of myelodysplastic, myeloproliferative diseases with platelet-derived growth factor receptor gene mutations. It is also used in the treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukemia types. Protein kinase inhibitors; They cause gastrointestinal disorders, edema, neurological and skin disorders, bleeding and various other side effects.

7.1. Imatinib: It acts by stopping Bcr-Abl tyrosine-kinase. In this case, it kills cancer cells by slowing down growth. Its use is used for gastrointestinal stromal tumors, hypereosinophilic syndrome, chronic myelogenous leukemia and acute lymphocytic leukemia. It is also applied in eosinophilic leukemia, systemic mastocytosis and myelodysplastic syndrome. Its side effects include fluid retention, gastrointestinal bleeding, bone marrow suppression, liver problems and heart failure (Anonymous, 2022al).

7.2. Ponatinib: It is a third-generation PTK inhibitor. It plays a leading role in the pathogenesis of acute lymphoblastic and chronic myeloid leukemia. It is effective against all mutant forms of the protein kinase called BCR-ABL, which is overproduced as a result of the formation of the Philadelphia chromosome in leukemia cells. In the forms of leukemia in which it is effective, it only kills the abnormal blood cells of patients carrying the Philadelphia chromosome (Ph+). It does not touch normal cells. In addition to all tested mutants of BCR-ABL, it also inhibits mutant PTK types other than BCR-ABL that are not affected by previous generation PTK inhibitor drugs. It is also effective against PTK mutant forms formed in solid tumor cells such as hormone receptor positive breast and endometrial cancer, and myeloma (Akıcı et al., 2012).

8. TOPOISOMERASE I INHIBITORS

The semi-synthetic alkaloid campothecin obtained from Campotheca acuminata, topotecan and irinotecan are in this group. These two bind to and inhibit topoisomerase I, one of the two topoisomerase enzymes that prepare the two DNA strands that are coiled in a supercoiled form in the intermitotic phase in the nucleus of the cell for replication before mitosis. Topoisomerase I breaks one of the two strands and temporarily corrects the helicity of the supercoil. In this way, it copies the DNA and allows the replication enzymes to approach the strand and perform their function. In those whose copying is completed, the two ends of the broken DNA strand that developed as a result of the break are joined together. The strands wrap around each

other again and become normal supercoils. The functions of topoisomerase I and II are essentially similar to each other. Topoisomerase breaks both DNA strands at once. Irinotecan and topotecan inhibit the topoisomerase I enzyme, stopping the division and reproduction of tumor cells and shrinking the tumor. Of these, irinotecan is effective alone or in combination with fluorouracil/folinic acid in metastatic colorectal cancer. It can also be combined with cetuximab in the treatment of metastatic tumors expressing epidermal growth factor receptor. It can also be used with fluorouracil/folinic acid and bevacizumab for the first-line treatment of metastatic colon and rectal cancer. It is also used with bevacizumab in the treatment of glioblastoma multiforme, with cisplatin in small cell lung cancer or as a single agent. Topotecan is used in metastatic ovarian cancer when first-line or subsequent treatment fails. It is administered with liposomal doxorubicin and paclitaxel in advanced ovarian cancer (Gür and Bilgiç, 2022). In addition, it is used as a second-line drug in the treatment of small cell lung cancer. Its dose-limiting side effect is bone marrow suppression. It can also lead to severe neutropenia and thrombocytopenia.

8.1. Irinotecan: It blocks the topoisomerase I enzyme, causing DNA damage and ultimately cell death. It is used with fluorouracil in colon cancer and cisplatin in small cell lung cancer (Bilgiç et al., 2022). Its side effects are blood clots, colon inflammation and allergic reactions (Anonymous, 2022am).

8.2. Topotecan: It prevents DNA replication and ultimately leads to cell death. This process leads to breaks in the DNA chain resulting in apoptosis. It is often used with paclitaxel as first-line treatment for ovarian, cervical and small cell lung cancer. Its side effects are myelosuppression, neutropenia, leukopenia, anemia and thrombocytopenia. Additionally, diarrhea, nausea, vomiting, stomatitis, constipation, increased susceptibility to infections and asthenia (Anonymous, 2022an).

9. MONOCLONAL ANTIBODIES

When monoclonal antibodies (produced by biotechnology methods) are applied as drugs using growth factors (GFs) or their receptors as antigens, they bind to them and block them. Thus, they create an antitumoral effect. They are immunological antagonists in terms of pharmacology.

9.1. Bevacizumab: They target the vessels that provide nutrients and oxygen to tumor cells. Since tumor cells reproduce uncontrollably, their need for nutrients and oxygen increases. The intravascular tissue growth factor recognizes and blocks the chemical signal that stimulates the growth of new blood vessels. It is used in metastatic colorectal and metastatic breast cancer, non-squamous cell non-small cell lung cancer. It can also be used off-label in metastatic renal cell cancer and high-grade glial tumors. It can cause serious gastrointestinal disorders including intestinal perforation and obstruction, cardiovascular disorders including hypertension and pulmonary hypertension,

neuropathy and dryness of the skin, and discoloration (Akıcı et al., 2012; Anonymous, 2020b).

9.2. Panitumumab: It is a monoclonal antibody that binds and blocks the epidermal growth factor receptor. It is used in the treatment of metastatic colorectal cancer where previous combination chemotherapy has failed. It can cause a hypersensitivity reaction during infusion.

9.3 Rituximab: It is a chimeric monoclonal antibody against the CD20 protein found on the surface of immune system B cells. When it binds to this protein, it triggers cell death. It is used for non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, idiopathic thrombocytopenic purpura, pemphigus vulgaris, myasthenia gravis and Epstein-Barr virus positive mucocutaneous ulcers. Side effects include reactivation of hepatitis B in previously infected patients, progressive multifocal leukoencephalopathy and toxic epidermal necrolysis (Anonymous, 2022ap).

9.4. Cetuximab: Indicated for head and neck and colorectal cancer. It is used in combination with radiation therapy in the treatment of head and neck squamous cell carcinoma. Side effects include increased incidence of reversible acne-like rashes, photosensitivity, hypomagnesemia due to magnesium loss and, less commonly, pulmonary and cardiac toxicity (Anonymous, 2022ar).

9.5. Trastuzumab: It acts by binding to the human epidermal growth factor-2 (HER2) receptor and slowing down cell replication. It

treats breast and stomach cancer. It is used specifically for cancer that is HER2 receptor positive. Its side effects are heart failure, allergic reactions and lung disease (Anonymous, 2022as).

9.6. Radioimmunoconjugates: They are monoclonal antibodies labeled with radioisotopes. They ensure that the radioisotope that will kill the tumor cell attaches to these cells, that is, directs the radioisotope to the target. Two drugs are used for this purpose.

9.7. Ibritumomab: It is an anti-CD20 monoclonal antibody labeled with Yttrium 90. It is especially effective in the treatment of low-grade non-Hodgkin lymphoma.

9.8. Tositumomab: It is an anti-CD20 monoclonal antibody labeled with iodine 131. It is effective in non-Hodgkin lymphoma.

10. OTHER CYTOTOXIC ANTINEOPLASTICS

10.1. Amsacrine: Prevents the production of new DNA by intercalation of DNA. It is used to achieve remission in acute myeloid leukemia that does not respond to treatment. Its dose-limiting side effect is bone marrow suppression.

10.2. Arsenic trioxide: It is used in cases of failure of combined chemotherapy containing retinoids in acute promyelocytic leukemia or relapse after treatment. It is a cardiotoxic drug and prolongs the QT interval on the ECG.

10.3. Bexarotene: It activates the retinoid X receptor (a cytoplasmic transcription) that is involved in cell reproduction and

differentiation. It is used in the treatment of skin T-cell lymphoma symptoms (in cases that do not respond to previous systemic treatment). It minimally suppresses the bone marrow and immune system. It causes hyperlipidemia, hypothyroidism, headache and skin rash.

10.4. Bortezomib: Inhibits proteasome-mediated protein degradation, which plays a role in the regulation of processes related to cell cycle, apoptosis and malignant transformation. It blocks the 20S catalytic subunit of the proteasome by binding to it. It induces apoptosis by inhibiting proliferation in multiple myeloma and mantle cell lymphoma cells. It causes peripheral neuropathy, thrombocytopenia, gastrointestinal disorders, pyrexia, fatigue and postural hypotension. It is under trial in the treatment of solid tumors.

10.5. Dacarbazine: Methylates guanine at the O-6 and N-7 positions. It acts by sticking methylated DNA chains together in a way that makes cell division impossible. It is used in the treatment of metastatic melanoma and soft tissue sarcomas within the junction. It is the element of the ABVD combination (doxorubicin, bleomycin, vinblastine and dacarbazine) used in the treatment of Hodgkin's disease. It causes significant bone marrow suppression and has a strong emetogenic effect. It can rarely cause liver vein thrombosis and related liver necrosis (Anonymous, 2022at).

10.6. Temozolomide: It is lipophilic and enters the brain tissue. It is used in astrocytoma grade IV, glioblastoma multiform grade IV (GBM IV), oligodendroglioma, anaplastic astrocytoma grade III and melanoma together with radiotherapy (Anonymous, 2022au).

10.7. Hydroxycarbamide: It prevents deoxynucleotide formation by inhibiting the ribonucleoside reductase enzyme, which is involved in the first steps of DNA formation. It has an S period-specific antineoplastic effect. It is used in sickle cell disease, essential thrombocythemia, chronic myeloid leukemia and cervical cancer. It increases fetal hemoglobin and reduces the number of attacks in sickle cell disease. Its side effects are bone marrow suppression and digestive system problems. It rarely causes nausea, vomiting, stomatitis and alopecia (Anonymous, aü).

10.8. Krisantaspas: It is an enzyme developed from Erwinia chrysanthemi and E. Coli. It catalyzes the hydrolysis of the amino acid asparagine into ammonia and aspartic acid. As a result, it reduces the asparagine stock. Since the asparagine synthase enzyme, which converts aspartic acid to asparagine in malignant cells, is deficient in leukemia types, these cells must take the asparagine they need to maintain their vitality from the blood. Asparaginase remains at a sufficient level in the plasma compartment for days. During this period, the asparagine in the plasma is converted to aspartic acid by this enzyme. As a result, the tumor cell is destroyed due to asparagine in the blood in vitality, RNA, DNA and protein synthesis. This drug is period-specific and shows its effectiveness in the Gj period. Asparagine is also required for some normal tissue cells, even if not at the tumor cell level. Krisantaspas is used in the treatment of acute lymphoblastic leukemia. It also has a place in the treatment of lymphoblastic lymphoma. Its superiority over other drugs is that it does not suppress the bone

marrow. It is usually combined with antineoplastics such as prednisone and vincristine.

Side effects; Coagulation disorders due to inhibition of the production of coagulation elements and antithrombotic elements, bleeding, thrombosis and pancreatitis. In addition, hyperglycemia due to the disruption of insulin synthesis, hypoalbuminemia due to the disruption of albumin synthesis and allergic and anaphylactic reactions.

10.9. Mitotane: It is selectively cytotoxic in adrenal cortex cells. It is used in the treatment of Cushing's syndrome and inoperable adrenocortical cancers. It is a very toxic drug. The effectiveness of the treatment is determined by monitoring the excretion of free cortisol in the urine. External hydrocortisone is applied to eliminate the decreased cortisol level. Its most important side effects are nausea, vomiting, anorexia, neurotoxicity, hypogonadism, gynecomastia and thyroid disorders.

10.10. Pentostatin: The enzyme is found in all lymphoid cells, but the highest level is detected in T cells. Inhibition of the enzyme causes the accumulation of deoxyadenosine triphosphate in the tumor cell, inhibiting cell proliferation. It is used intravenously in the treatment of hairy cell leukemia. It is also used in steroid-resistant acute and chronic graft-versus-host disease and relapsed chronic lymphocytic leukemia. It is a very toxic drug (Anonymous, 2022av).

10.11. Temoporfin and Porfimer sodium: When the two drugs accumulate in malignant tumor tissue and are activated by laser beams, they have a cytotoxic effect and kill the tumor cells. This type of

treatment is called photodynamic therapy. It is used to treat small cell lung and advanced head and neck squamous cell and obstructive esophageal cancer.

10.12. Procarbazine: It is lipophilic and can enter the brain. It is applied with vincristine, chlormethine and prednisone in Hodgkin's disease. It is applied with vincristine and lomustine in brain cancers similar to glioblastoma multiforme. Side effects are low blood cell count and vomiting. It also causes depression and fatigue. It should not be used in those with kidney and liver problems (Anonymous, 2022ay).

10.13. Thalidomide: It is an immunomodulator. It works by stimulating T cells and reducing TNF-a synthesis. It is applied with melphalan and prednisolone in multiple myeloma. It is also used in leprosy complications and graft-versus-host disease. Side effects are blood clots, peripheral neuropathy and tumor lysis syndrome. It is strongly teratogenic (Anonymous, 2022az).

10.14. Lenalidomide: It is an immunomodulator, antineoplastic and antiangiogenic agent. It is used with dexamethasone after other treatment in multiple myeloma. It also treats myelodysplastic syndromes. Its side effects include diarrhea, itching, joint pain, fever, headache and sleep problems. It can also cause venous thromboembolism and severe neutropenia. It is also teratogenic (Anonymous, 2022aaa).

10.15. Trabectedin: It is used in advanced soft tissue sarcoma and ovarian cancer when treatment with ifosfamide and anthracyclines

fails or is contraindicated. Since it has hepatotoxic and strong emetogenic effects, it is infused with dexamethasone to prevent them.

10.16. Tretinoin: The observation that vitamin A deficiency leads to metaplasia and neoplasm has led to the development of strong vitamin A analogs as antineoplastic drugs. It is used alone or together with chemotherapy in the induction of remission and the treatment of acute promyelocytic leukemia. With this use, both the remission rate and disease-free survival have been found to be superior to standard AML treatment. In this disease, the "promyelocytic leukemia gene" and the "retinoic acid receptor a gene" located on different chromosomes have come together with reciprocal translocation to form a new fusion gene. Since retinoic acid receptors are insufficient in the myeloid tissue, myeloid cell maturation stops at the promyelocyte stage. In this way, the clinical picture of acute promyelocytic leukemia occurs. Overstimulation of the insufficient number of receptors by administering tretinoin in the form of a drug eliminates this disorder and allows promyelocytes to differentiate and mature (Aktaş et al., 2024).

11. HORMONES AND HORMONE ANTAGONISTS

It is known that 25% of tumors in men and 40% in women are hormonally based. This treatment is treated without cytotoxicity. It is applied in breast, endometrium and prostate treatment. It aims to prevent the growth of cancer cells.

11.1. Hormone synthesis inhibitors: They prevent hormone production. Aromatase is the enzyme responsible for converting androgens into estrogen in women during menopause, and aromatase inhibitors inhibit this enzyme, reduce the amount of estrogen and prevent cell growth. The use of drugs such as anastrazole and letrozole in the treatment of breast cancer patients has reduced deaths due to this disease. Gonadotropin-secreting hormone analogs are used in the treatment of prostate and ovarian cancers, and chemical sterilization is applied to the organs (Gur & Aktaş, 2020).

11.2. Hormone receptor antagonists: They bind to hormone receptors in the cell and prevent the binding of that hormone and stop cell growth. They are divided into two groups: anti-estrogens and anti-androgens. They are known as selective estrogen receptor modulators. Tamoxifen, toremifene and fulvestrant are used in the treatment of hormone receptor-positive breast cancer.

11.3. Hormone supplementation: When the level of a hormone increases, another hormone steps in and blocks it, or vice versa. In some cases, they create a cytotoxic effect on cancer cells by giving hormones from outside. Synthetic progestogens similar to progestin are used in endometrial, breast and prostate cancers. Synthetic estrogens similar to diethylstilbestrol treat prostate cancer by suppressing testosterone production (Erdoğan, 2020).

11.4. Glucocorticoids: They create a lympholytic effect by preventing proliferation in lymphoid tissue. In addition, they prevent the growth of mesenchymal tissue. They are applied for the treatment

of acute lymphoblastic or acute undifferentiated leukemias and non-Hodgkin and Hodgkin lymphomas and multiple myeloma. In addition, they are used to reduce the side effects caused by other drugs. For example, they are used as a synergistic effect with antiemetic drugs in vomiting due to chemotherapy. In addition, they provide vascular wall stabilization in bleeding due to thrombocytopenia. In addition, they are used for liver protection purposes together with hepatotoxic drugs. Prevention of edema formation or elimination of edema in areas where tumor-related edema creates problems (brain and mediastinum) during radiotherapy or at the time of diagnosis. Treatment of hypercalcemia due to paraneoplastic or bone metastases. Suppression of the anterior pituitary lobe. Correction of glucocorticoid hormone deficiency caused by chemical adrenalectomy. Treatment of allergic-anaphylactic reactions due to antineoplastic drugs. They are also used for the prevention and treatment of fibrosis (Aktaş & Yahyazadeh, 2022).

11.4.1. Prednisone: It is used in combination with cancer drugs in acute lymphoblastic leukemias, non-Hodgkin lymphomas, breast cancers, adrenal cortex tumors and multiple myelomas. It prevents cell proliferation by inhibiting protein synthesis. Prednisone is used in high doses in antitumor treatment. Therefore, the frequency and severity of side effects increase. It creates a tendency to diseases due to water and salt retention, gastric irritation, hyperglycemia, hypertension, moon face, osteoporosis, and immunosuppressive effects. They also cause atrophy in the adrenal cortex (Akıcı et al., 2012; Dökmeci & Dökmeci, 2016).

11.5. Estrogens: Tamoxifen is used in the treatment of breast cancer, and ethinylestradiol is used in the palliative treatment of prostate cancer.

11.5.1. Tamoxifen: It is a selective estrogen receptor modulator. Cancer cells require estrogen for their development. It prevents the spread of cancer by stopping estrogen receptors in breast tissue. It also has angiogenesis (vascularization) stopping properties. With this property, it is also applied in many types of cancer. In addition, it is also applied in the treatment of brain damage that develops in radiation therapy (Anonymous, 2021b).

11.6. Progestogens (progestins): They are used in the treatment of endometrial cancer with their antiestrogenic effects. Estrogens have a proliferative effect in the endometrium. Progestins, on the other hand, prevent proliferation, mature the cell and promote apoptosis. They have limited effectiveness in breast and prostate cancers. The most commonly used progestins in the treatment of cancer; megestrol acetate, norethisterone and medroxyprogesterone acetate. Due to their antiandrogenic effects, they are used in the treatment of cachexia and anorexia due to cancer.

11.6.1. Megestrol acetate: It is an appetite-stimulating progestin. It has also been used in the treatment of breast and endometrial cancer and in birth control. Side effects include increased appetite, weight gain, vaginal bleeding, nausea, edema, low sex hormone levels, sexual dysfunction, osteoporosis, cardiovascular complications, and glucocorticoid effects (Anonymous, 2022aab).

11.6.2. Medroxyprogesterone: Progesterone derivatives are effective in endometrial cancers with their antiestrogenic effects. Medroxyprogesterone acetate and hydroxyprogesterone caproate are the main antitumor progesterone preparations (Dökmeci & Dökmeci, 2016).

11.7. Antiestrogens: They are selective estrogen receptor stimulators that competitively block estrogen receptors on target cells. Toremifene and tamoxifen citrate inhibit the aromatase enzyme that catalyzes the conversion of androgenic estradiol precursors to estradiol in the ovary and non-ovarian tissue. The main ones are formestane, exemestane, anastrozole and letrozole. They are used in the treatment of breast cancer in women.

11.7.1. Toremifene: It is a selective estrogen receptor modulator and therefore a mixed agonist-antagonist of the estrogen receptor (ER), which is the biological target of estrogens. For example, estradiol has estrogenic effects in bone, liver and uterus and antiestrogenic effects in breasts. It is used in the treatment of advanced breast cancer in postmenopausal women. Side effects include vaginal discharge and bleeding. It can also cause blood clots, irregular heartbeats, cataracts, visual disturbances, increased liver enzymes, endometrial hyperplasia and endometrial cancer (Anonymous, 2022aac).

11.8. Gonadorelin analogs: It has a decapeptide structure. Gonadotropin-releasing hormone (GnRH) is released pulsatile from the hypothalamus. It is transported to the anterior pituitary gland and from there it ensures the release of gonadotropins LH and FSH. Long-acting

synthetic GnRH preparations stop gonadotropin secretion by causing desensitization in the pituitary gland after temporary stimulation. They are used in the treatment of prostate cancer.

11.9. Gonadotropin-releasing hormone antagonists: It is a hormone antagonist called Degarelix. It is used in the treatment of advanced prostate cancer.

11.10. Antiandrogens: Flutamide, cyproterone acetate, bicalutamide and nilutamide. They block testosterone receptors and eliminate the effects of androgens of testicular or adrenal origin on target cells. They are used alone in the treatment of advanced prostate cancer or together with GnRH analogs to prevent flare-ups that may occur in the first week of treatment. Nilutamide has the most gravimetric effect and is the most selective for testosterone receptors.

11.10.1. Nilutamide: It is a non-steroidal antiandrogen used in the treatment of prostate cancer. It acts as a selective antagonist of the androgen receptor (AR). It prevents the effects of androgens such as testosterone and dihydrotestosterone (DHT) in the body. Most prostate cancer cells need this hormone for growth and survival. Nilutamide can prolong the life of patients by slowing the progression of prostate cancer. Side effects in men; breast tenderness and enlargement, feminization, sexual dysfunction and hot flashes. It has been replaced by new drugs such as bicalutamide and enzalutamide (Anonymous, 2022aad).

11.10.2. Flutamide: They block testosterone receptors on target cells and inhibit the effects of testicular and adrenal (adrenal)

androgens. They are used in the treatment of metastatic prostate cancer. Side effects: Hot flashes, decreased libido and impotence. (Dökmeci & Dökmeci, 2016).

11.11. Somatostatin analogs: It is a hypothalamic hormone that inhibits the secretion of growth hormone from the anterior pituitary. Somatostatin analogs (octreotide and lanreotide) treat pituitary tumors that secrete growth hormone (as in acromegaly). They also treat neuroendocrine tumors. In addition, lanreotide is used in the treatment of thyroid tumors by intravenous infusion or deep subcutaneous injection of a depot gel preparation. Octreotide is used to prevent complications in pancreatic surgery, esophageal variceal bleeding, and vomiting in the elderly.

11.11.1. Lanreotide: It is used in the treatment of acromegaly due to both pituitary and nonpituitary growth hormone-secreting tumors and in the treatment of neuroendocrine tumors, especially carcinoid tumors. It is also indicated in the treatment of thyrotrophic adenoma, a rare tumor of the pituitary gland that secretes TSH. It is used in the treatment of unresectable, well- or moderately differentiated, locally advanced, or metastatic gastroenteropancreatic neuroendocrine tumors. It also finds application in polycystic liver disease (Anonymous, 2022aae).

12. OTHER APPROACHES IN CANCER TREATMENT

12.1. Radioisotopes Radioactive phosphorus (32P): It is prepared in the form of sodium phosphate solution. It is used in the

treatment of polycythemia vera and other myeloproliferative disorders and chronic lymphocytic leukemia. The radioactive half-life of 32P is 14 days. It deforms cells with the beta rays it emits. These rays affect a 2 mm area in the tissue. 32P phosphate is processed as stable phosphate in the body. It accumulates in cells where proliferation is rapid, especially normal bone marrow cells and neoplastic cells, and in the bone. Phosphate tumover is high in these areas. Radioactive phosphate is administered orally or intravenously at a dose of approximately 3 millicuries per day for five days. If a high dose is applied, it causes obvious depression in the bone marrow. Apart from this, it is at the last rank among treatment alternatives because it increases the risk of developing secondary leukemia.

12.2. Radioactive iodine (132I): It is prepared in the form of sodium iodide solution. It is concentrated by being retained by normal or malignant thyroid cells similar to cold iodine. It is collected in the colloid within the thyroid follicles. Thyroid cancer metastases also retain iodine in the same way. 132I causes damage to thyroid or tumor tissue with the beta rays it emits. Its radioactive half-life is 8 days. It is used orally or intravenously in thyroid cancer cases. 125I can also be used instead of this radioisotope for the same indications. The radioactive isotopes mentioned emit gamma rays (radioactive iodine) and X-rays (radioactive phosphate) in addition to beta rays with antineoplastic activity. Protective measures should be taken by healthcare personnel who administer gamma ray emitters.

12.3. Strontium 89: It is applied instead of radiation therapy in prostate cancer with multiple bone metastases. It is a palliative approach for pain.

12.4. Immunotherapy: It is the strengthening of the immune system against cancer. This work is applied as passive immunotherapy, active immunotherapy or adoptive immunotherapy. Finally, immune system cells with increased tumoricidal effectiveness are applied to the person. This treatment is applied after chemotherapy. First, Corynebacterium parvum and BCG vaccines are applied. In recent years, human interferon-alpha, interleukin-2, anti-T antibody, tumor necrosis factor-alpha (TNF-a) and autologous LAK cell suspensions made with DNA recombination technology have begun to be investigated in certain cancers. Of these, interferon-alpha has entered the routine treatment of hairy cell leukemia. Biological response modifiers, cytokines and other immunotherapeutics, monoclonal antibodies and antibody conjugates have been used in cancer treatment (Aktaş et al., 2021).

12.4.1. Cytokines: They are a component of proteins and peptides synthesized by plant and animal cells that enable cells to communicate with each other. They perform their functions through cell surface cytokine receptors. They are formed by macrophages, active lymphocytes, endothelium, epithelium and connective tissues in immune and inflammatory reactions. Their release is temporary. They bind to receptors in the cell and stimulate cell reproduction. They are released in various infection, immune and inflammatory disorders.

While the immune system is fighting a pathogen, cytokines signal immune system cells such as macrophages and T cells and allow them to reach the infection site. Cytokines stimulate them to synthesize more cytokines and make these cells effective. They are synthesized by different cells and are effective in the cell's surroundings and the whole organism (Anonymous, 2021c). They are synthesized with recombinant DNA technology and applied as a drug. These include interleukins, lymphotoxin, tumor necrosis factor-alpha and colony-stimulating elements. Of these, interferon alpha-2a and alpha-2b subtypes are applied in certain types of cancer. Structurally, there is an amino acid difference between the two. Interferon-alpha destroys the proliferation of some tumor cells by directly acting as a cytotoxic agent. In addition, it strengthens the cellular immune defense against tumor cells by increasing the proliferation and effectiveness of macrophages, interferons and natural destroyer cells. Interferon-alpha-2a is applied in the treatment of hairy cell leukemia. Its therapeutic effectiveness in this disease is strong. It is effective in chronic myelocytic and lymphocytic leukemia, non-Hodgkin's and cutaneous T-cell lymphoma, hematological neoplasms and solid tumors such as malignant melanoma, multiple myeloma, AIDS-related Kaposi sarcoma, renal cell cancer and carcinoid tumor (Akıcı et al., 2012).

12.4.2. Aldesleukin (IL-2): It is a protein secreted by mature T lymphocytes and causes the proliferation of other T lymphocytes. When it was first discovered, it was called T cell activation factor. They also activate cytotoxic T and natural killer (NK) cells. In addition, they convert non-B non-T “null” lymphocytes into lymphokine-activated

destroyer cells. NK cells create a spontaneous destructive effect against allogeneic and autologous target cells. They kill target cells by lysis without the need for prior sensitization and the mediation of major histocompatibility antigens. Their cytolytic effect is stimulated by IgG and IL-3 antibodies. In addition, they secrete various lymphokines that play a role in immunoregulation. Aldesleukin does not touch normal cells and its usual target cells are virus-infected cells and cells that have undergone malignant transformation. For this reason, they perform immune surveillance in destroying malignant transformation and metastasis foci and constitute an important element of the immune reaction against viral infections. IL-2 obtained by DNA recombination technology is applied in metastatic malignant melanoma and metastatic renal cell cancer. It reduces tumor volume in some individuals. But it does not prolong survival. It has high toxicity.

Side effects are hypovolemia (increased capillary permeability), hypotension, development of edema in the lungs and tissues. In addition, azotemia is acute respiratory syndrome.

12.4.3. Autologous LAK cell + aldesleukin injection: It is an adoptive immunotherapy method. Lymphocytes taken from the patient via apheresis are transformed into LAK cells by incubating them with aldesleukin outside the body. Prepared autologous LAK cells are infused into the patient who is given IL-3 for five days. It is applied in the treatment of metastatic solid tumors that do not respond sufficiently to classical treatment. It is a relatively toxic application. It can cause severe fluid retention and pulmonary edema.

12.4.4. Adoptive immunotherapy method: It is to isolate and multiply tumor-infiltrated lymphocytes from surgically removed tumor tissue and then give them to the patient by i.v. infusion.

13. APPLIED PHARMACOLOGY OF ANTINEOPLASTICS

Approaches to the treatment of neoplastic disorders:

13.1. Surgical intervention: It is preferred in cases where there is no metastatic condition and the primary tumor is completely removed. Although it varies with factors such as the type and stage of the tumor, the addition of other treatments to surgical treatment prolongs survival in many types of tumors and minimizes the risk of unnecessary tissue damage.

13.2. Radiation therapy: It is a physical means to kill cancer cells. It is ionizing radiation applied to a part of the body or to the whole body. Radiation kills cancer cells directly or genetically alters them and directs them to apoptosis.

13.2.1. Stereotactic ablative radiotherapy: It is the damage and destruction of selected areas in an organ or tissue by ionizing radiation. It exposes a very small area of the body to a very high radiation dose. It is preferred in cases of brain tumors and in cases where the patient's condition cannot tolerate surgery.

13.2.2. Gamma knife systems: Average gamma rays are applied to treat small tumors. Many radiation beams come together to concentrate on the treated cell mass and high dose radiation is applied.

13.2.3. Linear accelerator systems: High energy x-rays are applied. It treats larger tumors and larger affected areas than gamma. Areas other than the brain can be treated with this.

13.2.4. Intensity-modulated radiation therapy: In breast, brain, prostate and head and neck cancers, radiation is given to this area at different strengths and protects the vital area from radiation.

13.3. Chemotherapy: It is to stop the reproduction of tumor cells with chemical agents and kill them. Side effects; hair loss, nausea, fatigue and vomiting develop. Strong chemotherapy can weaken the immune system in patients and cause death (Erdoğan, 2020).

13.3.1. Antineoplastic drug combinations: Treatment with drug combinations is a common approach in cancer chemotherapy. Single drug therapy applied in more limited indications is less toxic and allows for the testing of more drugs if necessary.

Advantages of combination therapy:

1. Provides a more powerful attack treatment. Since the drugs in the combination are selected from among drugs with different types of toxicity, they exhibit additive or synergistic antineoplastic interactions. However, their toxicity is not additive,

2. Has a higher probability of causing a longer-lasting cure,

3. Reduces the risk of tumor cell resistance,

4. Has a higher potential for cure.

The following principles are taken into account when combining drugs against a specific tumor type:

1. Each drug should have been tested alone and found effective in a sufficient number of patients in the intended indication. The most effective of these should be selected.

2. The mechanisms by which the drugs kill the tumor cell should be different. The benefit of this is the reduction of the possibility of tumor cell resistance and the potentiation of therapeutic efficacy. Antineoplastic combinations usually include classic alkylators, antibiotic-type drugs, a specific alkylator such as cisplatin, dacarbazine and procarbazine, an antimetabolite and a mitotic poison drug. In leukemias and lymphomas, a glucocorticoid drug such as prednisone is often added.

3. The toxicity of the drug, especially dose-limiting toxicity, should not be on the same system. This is important in allowing each drug to be administered at full dose and obtaining a strong effect, and in reducing the possibility of resistance development. Vincristine, bleomycin, alt'retamine, crisantaspas, high-dose methotrexate administered with calcium folinate, glucocorticoids and some other drugs have practically no toxic effect on the bone marrow. Therefore, they are suitable for combination with bone marrow suppressant drugs.

4. The administration of the drugs included in the combination should be optimally timed within each cycle. In the timing or sequencing of drugs within the cycle, priority is given to the non-period-specific drug and the cycle is started with it. In this way, tumor

cells are allowed to shrink the tumor after their effects have worn off. Sensitivity to period-specific drugs to be administered within the same cycle is increased. Another approach to timing is to suppress tumor proliferation by administering high-dose methotrexate with bleomycin, vincristine, prednisone, or calcium folinate during the resting period between doses of myelotoxic drugs. Other cytokinetic periods may also affect the order of drugs within the cycle. For example, the increase in DNA synthesis that becomes apparent approximately 10 days after the first dose of the S-period-specific drugs cytorazine and methotrexate is the most favorable period for the administration of second doses.

5. They cause fractional or exponential cell death. Therefore, chemotherapy should be repeated at certain intervals. The drug-free period is adjusted according to the recovery time of the organ most sensitive to the toxicity of the drugs included in the combination, usually the bone marrow. Autologous stem cell application and the administration of hematopoietic growth factors allow chemotherapy cycles to be administered on time without delay. 6. Beneficial and harmful interactions between drugs should be taken into account in the design of combinations. The effect of one drug should be prevented from being impaired by pharmacokinetic, cytokinetic and biochemical interactions. An example of a pharmacokinetic interaction is to avoid combining a drug that is eliminated by the kidney with another drug that is nephrotoxic, to carefully monitor the patient's renal function in cases where it is necessary, to hydrate the patient if there is no problem before administering the nephrotoxic drug, and to adjust the dose of the drug excreted by the kidney by measuring plasma levels, if possible.

Methotrexate, if given at least 1 hour before fluorouracil, increases the conversion of fluorouracil to its active nucleotide form in the tumor cell and its effectiveness. In contrast, if fluorouracil is given first, an antagonistic interaction occurs. The thymidylate synthase pathway is blocked and intracellular folates accumulate as tetrahydrofolate in the cell, and methotrexate cannot be effective. This is an example of a biochemical interaction. We can consider the application of these principles with an example. All of the drugs included in the MOPP (mechlorethamine + vincristine + procarbazine + prednisone) combination are effective against Hodgkin's disease on their own. However, when used as a single drug, the response rates to treatment are low. However, with the combination, complete remission is achieved in approximately 80% of patients and cure is achieved in more than 50%. Both the mechanisms of action and the dose-limiting toxic effects of the drugs are different. While the myelotoxic effects of mechlorethamine and procarbazine are prominent, vincristine and prednisone do not suppress the bone marrow (Akıcı et al., 2012; Aktaş et al., 2020d).

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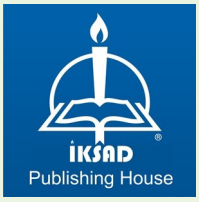

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