CHEMOTHERAPY TOXICITY EFFECTS IN CANCER

Tuğçe BİLKİ

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PREFACE

Cancer is a fatal disease that we frequently encounter today and is caused by mutations that may occur in many genes. If the cancer resulting from these mutations cannot be stopped, it can quickly spread through the organs by metastasis. Treatment of cancer is planned according to its stage, type, and how the patient responds to treatment. Patients can be treated via surgery, chemotherapy, immunotherapy, or/and targeted treatments. Chemotherapy is the most used method to rapidly stop the spread and proliferation of cancer cells, shrink tumors, and reduce the fatal effects caused by cancer. Cancerous cells are treated with chemotherapy drugs given to patients. However, studies show that in the chemotherapy treatment, healthy cells are also damaged, causing toxicity. Although chemotherapy treatment significantly increases the chances of survival in patients, the toxicities that occur can sometimes be fatal and or force the treatment to halt. While toxicities that occur may have temporary effects that alleviates after the treatment, there are also toxicities that cause permanent damage to the patients. In this book, types of colon, stomach, liver, kidney, pancreatic and spleen cancers are examined and the toxicities that occur in common chemotherapy treatment are examined.

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INTRODUCTION

Cancer is a fatal disease that may begin with the abnormal proliferation of healthy cells. There is the effectiveness of some specific factors in the development of this disease environmental factors that the person is exposed to throughout his life, stress, nutritional habits, diseases, and infections caused by bacteria and viruses are included in (P. Anand et al., 2008; Patel, 2012). According to the GLOBOCAN cancer data platform created by the World Health Organization's International Agency for Research on Cancer (IARC), an estimated 19.3 million cancer cases were detected and approximately 10 million people died due to cancer in 2020 (Chhikara & Parang, 2022). Common types of cancer diagnosed worldwide include breast, lung, liver, stomach, prostate, colon, and pancreatic cancer. Cancers with a high mortality rate in women include breast, lung, and cervical cancer. Lung, prostate, and stomach cancer are common cancers with a high mortality rate in men (Chhikara & Parang, 2022).

Oncogenes and tumor suppressor genes are examples of genes that cause cancer cells to form when oncogenes are activated, cancerous cells are formed. However, when tumor suppressor genes are not active, cells become abnormal and begin to multiply, forming cancerous cells.

In many cases, it has been observed that cancer cells are formed because of multiple mutations in tumor suppressor genes, oncogenes, or microRNA genes, rather than in a single gene (Kontomanolis et al., 2020; Patel, 2012).

The function of proto-oncogenes, which are normal cellular genes that humans have, is to code for proteins that enable cell growth and differentiation. What proto-oncogenes create are chromatin remodelers, transcription factors, growth factors, and growth factor receptors, which are called signal transducers and apoptosis regulators. When these genes mutate, they may turn into oncogenes and, the existence of approximately fifty or sixty of these types of oncogenes has been discovered (Croce, 2008; Kontomanolis et al., 2020). An example of an oncogene point mutation is the *Ras* gene mutation. The mutated *Ras* genes cause excessive growth of the cells by encoding proteins that constantly transmit signals (Croce, 2008). As a result of this situation, uncontrolled gene expression occurs, which can result in cancer. On the other hand, it is now known that viruses can cause oncogene formation. It has been shown that DNA viruses and some RNA retroviruses can cause cancer in cells after infection. It has also been observed that chemical carcinogens are effective in the formation of oncogenes (Krump & You, 2018).

Another major factor in the development of cancer is the mutations of tumor suppressor genes. Tumor suppressor genes have the effect of stopping the excessive growth of the cells. Examples of these genes are the *RB1*, *P53*, *BRCA1* and *BRCA2* (Kontomanolis et al., 2020).The *P53* gene here is responsible for stopping the cell cycle. At

the same time, this gene triggers apoptosis and then initiates the self-destruction process because DNA is damaged. It has been observed that this gene is mutated in many types of cancer (Patel, 2012).

RB1 is a type of tumor suppressor gene, provides cell cycle and regulation. Mutation of the gene causes loss of function and resulting cancer. (Qin, 2023). It is a rare disease that occurs in the retina of the eye, usually seen in young children. In this type of cancer, mutations occur in the cells that are the precursors of the cone photoreceptors. As a result of the mutations, the tumor suppressor properties of the Retinoblastoma proteins are lost. There is a possibility of relapse in those who inherit this disease. They need to be followed for life and survival rates of patients can be increased with good treatment (Dimaras et al., 2015). *BRCA1* and *BRCA2* genes are involved in the DNA repair system by cooperating with other proteins in roles such as cell division and growth. Mutations in these genes especially increase the risk of breast cancer in women If there is a family member with this gene mutation, there is a possibility that it will be seen in other individuals as well (Hatano et al., 2020).

Healthy bodies host constant cycle of cell division and cell death. It is important for the organism to have its cells die at appropriate time. Apoptosis is the normal and controlled cell death for organism well-being and development. Apoptosis is different from necrosis, which is destruction due to damage. These include the destruction of old cells that can no longer perform their functions, their role in embryonic development and hormone-dependent cell destruction. In addition, factors such as DNA damage in the cell and the immune system can

also cause an apoptosis signal. Apoptosis is generally suppressed in cancerous cells. As a result, tumor cells grow and multiply rapidly (Morana et al., 2022).

Another way of cancer formation is the microRNAs which have been shown to play a role in the differentiation and growth of cells and cell metastasis. miRNA is non-coding messenger RNAs that play a role in gene expression (Ekanayake Weeramange et al., 2023). Additionally, miRNAs can function as oncogenic or tumor suppressors where the same miRNA can be oncogenic for one type of cancer and a tumor suppressor for another cancer (Ekanayake Weeramange et al., 2023; Reddy, 2015). When these functions are disrupted, miRNAs begin to become dysregulated. These changes in miRNA do not only occur in the tumor and its surroundings but also in body fluids (Ekanayake Weeramange et al., 2023). B-cell chronic lymphocytic leukemia was the first known cancer to be caused by miRNA abnormalities (Visone & Croce, 2009).

These cancer cells can enter the bloodstream and spread to other parts of the body. They create new tumors in new locations, this event is called metastasis. In addition, cancer cells can continue to grow by branching from existing blood vessels or creating new vascular access. This situation is called angiogenesis. As a result of angiogenesis, tumor cells are provided nutrients and oxygen by new veins and continue to grow (Kretschmer et al., 2021). As seen in Figure 1, tumor cells undergo metabolic adaptation to adapt to the metabolic stress they encounter which results in angiogenesis (Patel, 2012). Some factors stimulate angiogenesis such as vascular endothelial growth factor (VEGF),

fibroblast growth factor (FGF), angiogenin, angiotrophic, transforming growth factor (TGF α and β) and epidermal growth factor (Tobelem, 2007). For example, if VEGF is inhibited, tumor growth decreases with the decrease in vascularity (Tobelem, 2007).

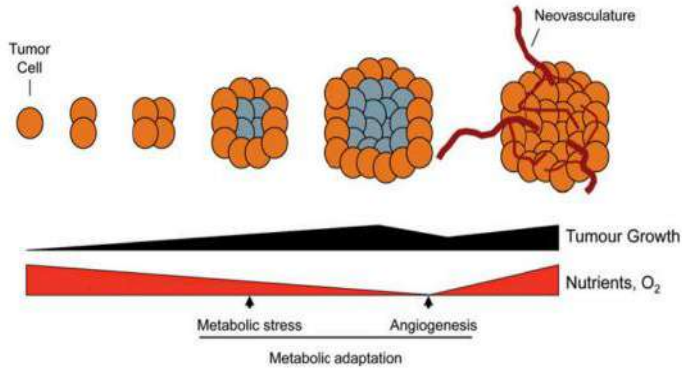

Figure 1. Growth stage of tumor cells**.** Tumor cells need nutrition and oxygen as they continue to grow. In the absence of nutrients and oxygen, tumor cells undergo metabolic stress and initiate angiogenesis. This situation is seen as a metabolic adaptation process that ultimately allows continuous growth of the tumor cells (Patel, 2012).

Cancer can occur in many parts of the body or can metastasize and reach different places (Kretschmer et al., 2021). For example, cancer cells can be seen to metastasize in the colon, stomach, lung, liver, kidney, and pancreas. During the metastasis process, cancer reaches these organs through the blood or lymph system (Langley & Fidler, 2007).

1. ANTI-CANCER DRUGS AND THEIR WORKING PRINCIPLES

Cancer cells, which manage to escape from the immune system with their differentiated mechanism and multiply uncontrollably, are a disease that progresses by metastasizing throughout the body and rapidly dividing and multiplying in the tissues in which they progress (Anand et al., 2023). If metastasis and advanced stage are not seen in patients, surgical methods are frequently used as treatment methods. Other methods used in patients other than surgery for treatment purposes include chemotherapy and radiotherapy treatments. The chemotherapy method stops the growth and division of cancer cells (Liu et al., 2021). In chemotherapeutic treatments, it is aimed to stop cancer with drugs. Cancer cells have their special metabolism. The differences in this metabolism are as follows; cell surface receptors receive signals more frequently, causing them to grow and proliferate uncontrollably (Anand et al., 2023).

Anticancer drugs used in cancer treatment are classified according to the mechanisms they act on and their origin. Alkylating drugs, one of the oldest drugs used in cancer treatment, bind to the DNA of cancer cells, and influence preventing the division and growth of those cells (Ogawa, 1997). It can occur in any phase of the cell cycle of the organism (Lehmann & Wennerberg, 2021). Its effect here is to damage DNA by cross-linking to DNA strands and prevent the transcription of RNA (Ogawa, 1997). As a result, the DNA mutates, and a cell destruction mechanism, called apoptosis, occurs. Alkylating agents are also known as antineoplastics. Alkylating agents are grouped

as nitrogen mustards, nitrosoureas, alkyl sulfonates, triazines, ethyleneimines, hydrazines, benzoquinone-containing agents, illudins and platinum-containing agents (Lehmann & Wennerberg, 2021).

Another class of anticancer drugs is antimetabolites. Antimetabolites have a growth-stopping effect by interfering with the cell's metabolism. Antimetabolites prevent DNA synthesis and change the structure of DNA. Since they are effective in many types of cancer, these drugs are still frequently used today (Lopez Perez et al., 2019). Pyrimidine-derived antimetabolites also interrupt RNA synthesis. Vinca alkaloids are obtained from the extract of the Vinca plant; It prevents cell polymerization, acts on tubulin, and prevents it from turning into microtubules, so that it cannot mix with the cytoskeleton, and is also a cell division inhibitor. Some predominantly used antimetabolite drugs are 5-fluorouracil (5-FU), 6-mercaptopurine, cytarabine, gemcitabine, and methotrexate (Langley & Fidler, 2007).

Another anticancer drug group is antitumor antibiotics. These drugs are not like ordinary antibiotics that treat infection. Their aim is to control cancer development, and generally, they affect the cell cycle and are divided into two types: specific and non-specific (Ye et al., 2022). Anti-tumor antibiotics, which are among the non-specific drug groups, stimulate the target tumor's DNA, preventing it from feeding the RNA. It is cross-linked to DNA strands. It prevents the growth of the cell by changing the structure of DNA. Examples of these drugs are doxorubicin, mitoxantrone and bleomycin. Specific drug groups progress more slowly and directly, and this group includes the drug Pingyangmycin. (Ye et al., 2022).

Another anticancer drug class includes topoisomerase enzyme inhibitors. These Topoisomerase I and II enzyme inhibitors are widely used in cancer treatments. (Liang et al., 2019). Enzymes that break the DNA chain of double-stranded DNA during the replication and transcription stages. By inhibiting these functions replication and transcription capabilities of cancer cells eliminated (Nitiss, 2009). Some examples for these commonly used drugs are etoposide, doxorubicin, daunorubicin, and mitoxantrone. Some of these drugs are obtained from plants or synthetically (Skok et al., 2020).

2. CHEMOTHERAPY

At the beginning of the twentieth century, some methods began to be tried to treat cancer. For this purpose, experiments were carried out by taking samples from some plant extracts. For example, the extract of the *Colchicum autumnale* plant was used to dissolve the tumor mass, it is one of the first plant extracts that used for cancer treatment (U. Anand et al., 2023). However, this plant is quite toxic in normal consumption due to the alkaloid colchicine it contains, and in case of poisoning it can cause lethal effects (Danilović et al., 2020). In later years, compounds obtained from plant extracts such as colchicine, vincristine and vinblastine began to be used for cancer cells (Anand et al., 2023). The idea of developing drugs using plant extracts or toxic compounds to treat cancerous cells, that is, the concept of chemotherapy, emerged first after seeing the lethal effect of the mustard gas on lymphatic tissues. Later, experiments were conducted on animals with this gas. When it was applied to the cancerous lymphoma tissues of animals, it was

observed that the disease regressed. This experiment paved the way for chemotherapy to treat cancer (Anand et al., 2023). In subsequent animal studies, treatment methods based on uracil intake were tried for non-hematological cancer types. As a result of this research, the use of 5-FU become one of the first therapeutic methods, that pioneers chemotherapy drug in the molecular therapy era (DeVita & Chu, 2008). Nowadays, methods such as targeted drug treatments and immunotherapy are rapidly developing for cancer treatment. However, although chemotherapy has known benefits and harms, it is still the most used treatment method for cancer (U. Anand et al., 2023).

Chemotherapy is a way of treating cancer by acting on cancerous cells using one or more anticancer drugs. This treatment aims to cure, reduce cancer symptoms, and destroy cancer cells by acting at the molecular level. Chemotherapy can be used in people with cancer at different stages of the disease. The drugs used in the treatment method may vary depending on the type of cancer (Alfarouk et al., 2015; Anand et al., 2023). Since cancer cells have much endogenous stress, applied chemotherapy drugs have the potential to destroy them faster than other cells (U. Anand et al., 2023).

Chemotherapy for cancer patients varies depending on the type of cancer and the stage of the patient (P. Anand et al., 2008). The treatment dose and duration applied are also very important (McKnight, 2003). If high doses of the treatment are applied, many side effects occur in the patients. That is why drugs are generally used at certain intervals so that the cells can renew themselves (U. Anand et al., 2023). In chemotherapy treatment, drugs are given to patients in various ways. For example,

intravenous chemotherapy is when the drug is given directly into a vein. Chemotherapy treatment can be given to patients at regular intervals as pills or liquids. Another injection method, intramuscular applications, is also included in this treatment (U. Anand et al., 2023). It is also seen that drugs are applied locally in some cases. For example, in treatment drugs administered directly the spinal fluid, or it is treated by administering intra-abdominal medication. Chemotherapy drugs, which are frequently used in cancer treatment, can be given to patients in combination with more than one drug to break the resistance of tumor cells. These medications are adjusted based on clinical data obtained from the patients (Nygren, 2001).

Cancer treatment is difficult to treat because the metabolic mechanism of cancer cells and the metabolism of host cells overlap. As seen in Figure 2, cancer cells interact with healthy cells. It is observed that some healthy cells die along with cancerous cells upon drug treatment (U. Anand et al., 2023). It is known that the treatment causes side effects, especially when rapidly dividing cells are commonly damaged, such as hair follicles and bone marrow cells (Lundqvist et al., 2015). As seen in part b of Figure 2, the cell cycle regulation is examined to have a significant effect on cancer cells. The curative effects of chemotherapy here are directed toward the proliferation, metastasis, and recurrence of tumor cells (Y. Sun et al., 2021). Current chemotherapy is based on the correct regulation of this cell cycle. Figure 2 shows which of these chemotherapeutic drugs act on the stages of the cell cycle, such as G0, G1, S, G2, M, and cytokinesis and all the

stages of the cell cycle here have different effects on the cell (Y. Sun et al., 2021).

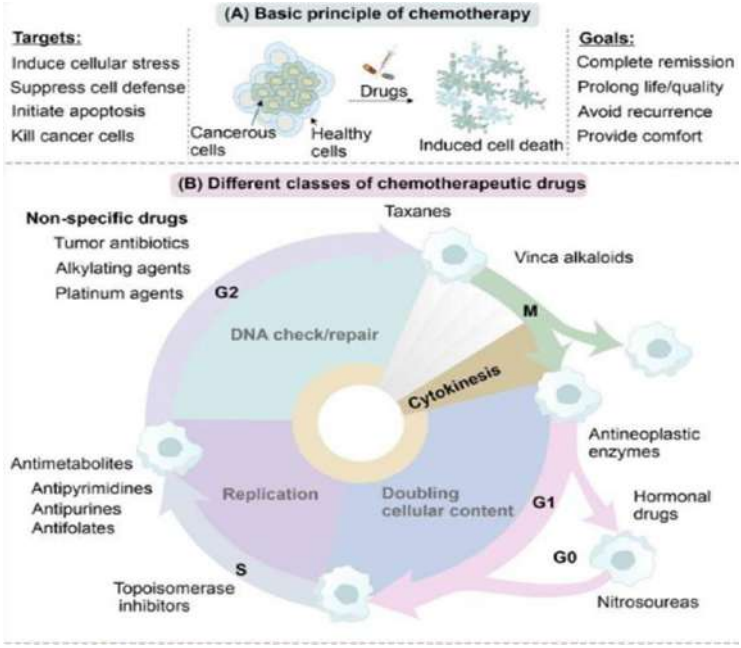

Figure 2. Basic principle of chemotherapy drugs and their effects on cell cycle**.** In the visual, part A explains the basic principle of chemotherapy. In part B, it is seen which stage of the cell cycle the drugs used in chemotherapy affect. (U. Anand et al., 2023)

In addition to the life-saving effects of chemotherapy treatment, the negative effects are too obvious to be ignored. Physical and psychological negativities occur in people who are exposed to these drugs for a long time. These effects can also be an obstacle for the patient to continue treatment. Studies are ongoing to minimize toxicities in patients (U. Anand et al., 2023).

3. WHAT IS TOXICITY?

Toxicology was known as the science of poisons in ancient times. Today's concept of toxicology examines the processes of absorption, distribution, metabolism, excretion, and how toxic substances become in living organisms, depending on the dose (Tsaioun et al., 2016). In other words, the science of toxicology is explained as the study of whether a substance causes harm to the organism, that is, its toxic effect. Specific interactions occur between chemicals and living beings that are exposed to them (Mückter, 2003). As a result of these interactions, the side effects and the poisoning may occur in living things. This is where the concept of toxicity comes into play. Toxicity examines the negative consequences of drugs on living things because of their chemical interactions (Mückter, 2003). Experimental studies have been conducted at *in vitro*, pre-clinical, *in vivo* and omics levels to examine these negative results (Yahya et al., 2021).

Paracelsus, a physician living in the sixteenth century, explained the dose-response relationship in substances. In his statement, he commented and documented that all substances can have toxic effects after a certain dose (Langman & Kapur, 2006). Toxicity that may occur when living organisms are exposed to various substances depends on the exposure time and the dose of the substance. In addition, the toxicity effect on the substance depends on toxicokinetic and toxicodynamic. Here, toxicodynamics deal with what the chemical does to the organism, and toxicokinetics deal with what the organism does to the chemical (Rozman & Doull, 2000). The consequences of toxicity can range from minor adverse effects to major adverse effects. For example,

impairment of organ function may cause the organ to fail to correctly function. The toxicity that occurs here is affected by factors such as absorption, distribution, metabolism, and excretion, which are also called ADME for short. At the same time, toxicity formation is affected by the interactions of substances such as drugs with cellular macromolecules (Yahya et al., 2021).

Toxicity may occur due to some chemicals or xenobiotics entering the body. In this case, the body will want to remove them because it sees them as poisonous (Tsaioun et al., 2016). Therefore, our body strives to reduce their absorption into the body, reduce their distribution to the body through the vascular system and remove them from the body through excretion. Predictions can be made about the toxicity of substances taken into the body with ADME information, and toxic effects can be minimized by drug development and clinical trials (Tsaioun et al., 2016).

There is an absolute relationship between the effects of drugs and the dose used. Dose descriptors are used when commenting on this relationship. The dose descriptive terms as EC_{50} (half maximal effective concentration), LD_{50} (lethal dose), ED_{50} (effective dose), LC_{50} (lethal concentration) are generally used (Arivazhahan, 2022). Additionally, the therapeutic index (TI) is the comparison of the dose rate of the drug used that has a beneficial effect with the dose rate that causes a toxic effect. It is used for reasons such as determining the most beneficial one among the drugs. This index is frequently used to reduce the negative effects caused by toxicity (Muller & Milton, 2012; Schneiderman et al., 1964).

The types of toxicity determination tests performed when toxicity occurs due to chemical drug doses administered to biological systems are classified as acute, subacute, and chronic toxicity. Acute toxicity is used to comment on LD_{50}. The LD_{50} refers to the dose that would be lethal in 50% of the tested population (Akhila et al., 2007). Acute toxicity is the harmful effects that occur after short-term exposure to a chemical or harmful substance. These effects may occur within one day. Sub-acute toxicity is the adverse effects that occur with repeated exposure to the chemical substance or harmful substance over 2-4 weeks. It is less severe than acute toxicity. Sub-chronic toxicity test doses are also determined through subacute toxicity studies. Sub-chronic toxicity occurs after approximately three months of exposure. It is less severe than acute and sub-acute toxicity (Kokova, 2023). Chronic toxicity involves a long exposure period of six months, and its effects may appear over the years. It has carcinogenic effects on humans. To examine and detect the effects of toxicity, changes in samples such as weight change, food consumption, skin, respiratory tract, cardiovascular systems, blood, and urine in the sampled creatures are examined (Kokova, 2023).

Phase research is performed on patients using the drug to measure and evaluate the toxicity values of drugs. Since these studies, the safe dose range is determined by examining the pharmacokinetic effects of the drug (Horstmann et al., 2005). Because even if drugs are tested on animals, they may not have the same effect on humans therefore, phase studies are needed (Hoering et al., 2011). In drug research, phase I trials are first conducted. Thanks to phase I studies, the safety of the drug is

tested, and the amount of dose-limiting toxicity is determined. These phase I studies are a precursor to the phase II research (Postel-Vinay et al., 2014). In the Phase II studies, the number of patients is increased to conduct more detailed examinations. The amount of drug to be used with the least toxic effect is determined by the studies carried out (Hoering et al., 2011).

4. TOXICITY EFFECTS OF CHEMOTHERAPY IN CANCER

Chemotherapy is one of the most established treatment methods that reduces the symptoms caused by cancer and prolongs the life of the person by stopping the progression of cancer. For this reason, despite its toxic effects, it continues to be actively used today (Nygren, 2001). The choice of drugs used in chemotherapy treatment varies depending on the type of cancer, its stage, and the response of patients to the drug. The purpose of these drugs is to treat cancerous cells and improve or eliminate the effects caused by the tumor. The dosage of the drugs used in the treatment and the response of patients is patients is crucial (U. Anand et al., 2023). When high doses or ineffective drug doses are given, which vary depending on the person, many side effects occur and this causes toxicity. In addition, in case of recurrence of the disease, there may be situations where cancerous cells do not respond to treatment after long-term exposure to drugs. Hence, exposure to greater amounts of chemotherapy increases the risk of toxicity and makes it difficult for the patient to continue treatment (U. Anand et al., 2023).

The metabolic processes of cancer cells, which is the process of converting nutrients into energy, are similar to normal cells (U. Anand

et al., 2023). Therefore, drugs used in chemotherapy treatment can damage different mechanisms and cells other than cancer cells. Examples of these mechanisms include blocking cell growth and, development to stopping DNA repair (Nygren, 2001). It is seen that most of the drugs used in treatment affect important cellular events. For this reason, chemotherapeutic drugs are also called cytotoxic agents because they cause many side effects. Serious adverse effects such as organ failure or organ loss due to toxicity are observed during treatment (U. Anand et al., 2023). In addition to these common side effects, nausea, vomiting, constipation, diarrhea, depression, anemia, fatigue skin and hair rashes may occur. For instance, behavioral toxicities attention deficit, memory problems, and lack of motivation can occur (U. Anand et al., 2023; Vichaya et al., 2015). In cases where chemotherapeutic drugs directly damage the bone marrow, the risk of infection or bleeding increases due to anemia. In another example, the negative effects on cardiovascular health resulting from the toxicity of chemotherapy treatment can be explained. During this process, chemotherapeutic drugs can negatively affect the functioning of heart cells and have vital consequences (U. Anand et al., 2023). Some toxicities encountered during chemotherapy may continue after treatment is terminated and may even leave permanent scars for life. It has been observed that the risk of mortality increases in cases of high symptoms encountered during treatment. The causes of the symptoms that occur are being investigated. However, neuroinflammation is an important focus in studies to explain behavioral toxicities such as fatigue and chemotherapy-induced cognitive impairment (CTCI)

(Vichaya et al., 2015). Neuroinflammation caused by cancer: It occurs through peripheral tissues or by damaging central nervous system cells. In addition, many other mechanisms exist and are being investigated to explain the toxicities that occur because of chemotherapy. For example, evidence has been found that mitochondrial dysfunction plays a role in the development of behavioral toxicities associated with chemotherapy (Vichaya et al., 2015).

4.1. Colon Cancer

Colon cancer is a serious type of cancer that can start in the colon or rectum. The large intestine, which is the last part of the human digestive system, is approximately one meter long. The colon is the part of the large intestine outside the rectum (Markowitz et al., 2002). Colon cancer is a type of cancer that can be treated when diagnosed early, depending on the stage of the disease (M. Ahmed, 2020).

Colon cancer has gained a place among common cancers in recent years. In colon cancer, cancer may develop in cases where patients do not show symptoms (F. E. Ahmed, 2003; M. Ahmed, 2020). This type of cancer can be diagnosed early by colonoscopy. Thus, mortality due to colon cancer was reduced. In addition, although there are non-invasive methods to diagnose this type of cancer, colonoscopy is very important due to its ability to directly visualize and diagnose (M. Ahmed, 2020; Ouyang et al., 2005). Some cancer organizations recommend that individuals undergo colonoscopy screening for control purposes after the age of 45. (A. M. D. Wolf et al., 2018). The risks of developing this cancer may vary due to environmental or genetic

factors. For example, being over 50 years old, obesity, that is, having a high-fat content, smoking and alcohol use, malnutrition, choosing low-fiber and high-fat foods, consuming excessive fried foods, and living a sedentary life without exercising are among these risk factors (F. E. Ahmed, 2003). When combined with excessive alcohol consumption and consumption of foods that do not contain folate, it can be seen as a significant combination that can lead to colon cancer (Giovannucci & Willett, 1994). Diseases that can be seen as risk factors in the formation of cancer include insulin resistance, kidney diseases, colorectal adenoma, inflammatory bowel diseases, ulcerative colitis and Crohn's disease, mutated MMR gene syndromes such as Lynch syndrome and Muir-Torre syndrome, or non-hereditary polyposis syndromes (Singh et al., 2014). It is also recommended that people with a family history of colon cancer or inflammatory bowel disease undergo screening (Finlay A Macrae, 2018). Genetic tests are of great importance in colon cancer, which occurs due to genetic factors. When genetic tests are positive, one should have a cancer screening test via colonoscopy every two years from the age of 20 until the age of 40 (Rex et al., 2009). Because these people are more likely to develop cancer than others (Finlay A Macrae, 2018).

4.1.1. Colon Cancer Mechanism

Colon cancer develops depending on the epithelial cells that form the inner surface of the intestine (Markowitz et al., 2002). In a normal person, these intestinal cells frequently renew themselves. However, in cells that can cause cancer, abnormal pools form during this renewal

and over time, they turn into cancer cells (De Santa Barbara et al., 2003; Sancho et al., 2004). These colon tumors are divided into right and left. Since there may be different structures in the same organ, this distinction is made based on their sources (Karabulut et al., 2021). Neoplastic tubular colon adenomas occur in colon neoplasia, which is a cancerous process. These have a stalked polypoid structure. These polyps are specially shaped tissue sizes formed in the intestinal mucosa membrane. As seen in Figure 3 A shows a normal mucosa of intestinal cells. These tubular adenomas are seen in Figure 3 B (Markowitz et al., 2002). After a while, the polyp acquires an irregular villous histological appearance, that is, the normal structure of the villous cells is disrupted, causing cancer or other diseases. This example of a villous adenoma is in Figure 3 C. Another tissue abnormality is dysplastic cellular cytology. The formation here may be associated with an increased risk of cancer (Markowitz et al., 2002). Another neoplasm found in the intestine is adenocarcinoma, which originates from mucus-producing cells. These are common cancerous cells in the large intestine (Labianca et al., 2010). Due to the high potential of premalignant colon adenomas, which are tissue abnormalities, to turn into cancer, their cancer can be treated in the early stages by surgical removal (Schoen, 2002; Smith et al., 2001). However, as with any type of cancer, there is a possibility of recurrence of colon cancer. The possibility of the recurrence of this colon cancer depends on the degree of attachment of the nodal involvement of the tumor in the intestinal wall. In other words, how deeply the cancer cells penetrate varies depending on how much they spread (Markowitz et al., 2002).

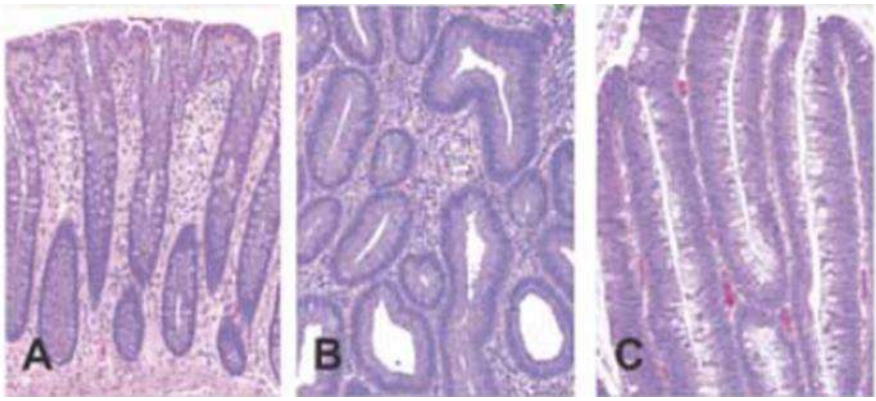

Figure 3. Image of cancer formation in intestinal cells**.** The cellular changes occurring in the intestine are depicted. In part A of the figure, the healthy intestinal cell structure is seen. A tubular adenoma is seen in part B of the figure. Abnormal growths begin to appear in the mucosa cells here. In part C of the figure, a villous adenoma is visible. As dysplasia increases in the cells here, villous structure formation is observed. These cells have a high probability of becoming cancerous (Markowitz et al., 2002).

Gene mutations also play an important role in the development of colon cancer. For example, adenomatous polyposis coli *(APC*), K-*ras*, *p53*, B-Raf proto-oncogene serine/threonine kinase, and mismatch repair gene mutations can lead to colon cancer (Ahmed, 2020). Hereditary colon cancer fails to function because of mutations in the *APC* tumor suppressor gene. These mutations cause adenomatous polyposis. As a result of this process, many colon adenomas form in the intestines, increasing the risk of cancer (Goss & Groden, 2000).

Additionally, tumor formation may occur with the activation of oncogenes due to chromosomal mutations. Mutations usually occur in the K-*RAS* and *BRAF* oncogenes. The mutated *KRAS* oncogene plays a role in the growth of cancerous cells in the colon (Malki et al., 2021). Studies show that vitamin D can prevent the growth of cancerous cells in the colon. In people with normal levels of vitamin D, vitamin D binds to the VDR signaling receptor, but in cases where this vitamin is deficient, the VDR signaling pathway becomes ineffective, which may result in colon cancer (Ferrer-Mayorga et al., 2019). It has also been observed that there are irregularities in the intercellular signaling pathways during the cancerous process of cells in the colon (Malki et al., 2021). Wnt/β-catenin, one of these signaling pathways, is responsible for the growth and differentiation of cells. As a result of mutations in the *APC* tumor suppressor gene, abnormalities in this signaling pathway may occur, leading to the formation of cancer cells (Ferrer-Mayorga et al., 2019). Moreover, studies show that chronic inflammatory bowel diseases play a role in the development of colon cancer (Terzić et al., 2010).

After cancer is diagnosed, it can be treated using endoscopic oncological and surgical methods, depending on its stage (M. Ahmed, 2020). The cancer screening tests are generally divided into two categories. These are visual and stool-based tests. (A. Wolf et al., 2018). Visual tests are colonoscopy, computed tomography (CT), colonography and flexible sigmoidoscopy. Stool-based tests contain the fecal immunochemical test, guaiac-based stool occult blood test, multi-

target stool DNA test, immunochemical tests such as Cologuard, mutant Kras and β-actin, and methylated BMP3 (A. Wolf et al., 2018).

4.1.2. Colon Cancer Treatment with Chemotherapy

Adjuvant and curative treatment methods are used to treat colon cancer. Curative treatment usually uses surgical methods to eliminate cancer. In addition to surgical methods, it also includes chemotherapy methods. Adjuvant therapy, which helps surgical methods, one of the cancer treatment methods, is also frequently used. Adjuvant treatment includes chemotherapy and radiotherapy methods applied after curative treatment against the possibility of cancer recurrence, even if there is no evidence of a tumor in the patient (Cienfuegos et al., 2018; Midgley, 2000). The purpose of chemotherapy, which is also applied in adjuvant therapy, is to destroy tumor cells that may occur anywhere in the body and have the possibility of metastasizing (Nygren, 2001).

In the treatment of colon cancer, curative resection, that is, surgical removal of the entire tumor, is considered the main treatment method for stages I and III of the disease (Edge & Compton, 2010). In an academic study conducted in 2018, it was observed that major complications developed after colon cancer surgery in stage I-III patients who underwent curative resection surgery and that the treatment also had negative aspects. These stage II and III patients were also administered 5-fluoropyrimidine chemotherapy drugs (Cienfuegos et al., 2018). Examples of these major complications include pneumonia, intra-abdominal abscess, septicemia, bleeding, and acute renal failure. It was observed that the local and peritoneal recurrence

rates in patients with these major complications were higher than in those without complications, and on the other hand, the systemic recurrence rates were the same in both groups. As a result of this process, it was observed that the survival rates in patients who experienced major complications were lower than those who did not experience complications (Cienfuegos et al., 2018).5-FU, is a chemotherapy drug that is one of the oldest drugs frequently used in the treatment of colon cancer. This drug is a prodrug that inhibits thymine, DNA and RNA synthesis. This drug is given to the body through the portal vein in cases of metastasis during colon cancer treatment (Midgley, 2000). During the portal vein, the drug will reach the liver directly without being metabolized through the vein. The drug reaching the liver is in higher concentration because it is not metabolized. This increases the effectiveness of the drug. One of the advantages of this method is that the drug does not spread to other organs, reducing systemic toxicity (Midgley, 2000).

While surgery is recommended for patients in Stage II, there are cases where adjuvant treatment is not recommended, although it generally varies from patient to patient (M. Ahmed, 2020). In the case of patients in advanced stages such as Stage III, combined drugs consisting of FOLFOX regimen, i.e. oxaliplatin and fluoropyrimidine, and FOLFIRI, i.e. leucovorin and irinotecan, are used. Although long-term toxicity effects occur because of the use of these treatment drugs, they continue to be used because they improve survival rates (Taieb & Gallois, 2020). Additionally, CAPOX combined with capecitabine and oxaliplatin, is among the adjuvant chemotherapy methods for stage III.

In the IV stage of colon cancer, combination chemotherapy drugs such as FOLFIRI, FOLFOX, CAPIRI, and CAPOX, which is a combination of capecitabine and oxaliplatin, are frequently used (M. Ahmed, 2020). Cancer treatment, in addition to monotherapy, which is a chemotherapy drug combination, also includes methods such as biologically targeted therapy, immunotherapy, palliative surgery, and radiotherapy(Benson et al., 2017).

4.1.3. Chemotherapy Toxicity Effects in Colon Cancer

Chemotherapy is a treatment that targets tumor cells, although it destroys tumor cells, it has toxic effects on healthy cellular tissues (Rühle et al., 2018).

Oxaliplatin chemotherapy drug usually causes neurotoxicity as a side effect in patients. Neurotoxicity occurs due to damage to the nervous system. For example, increased stimulation of axons and changes in sodium-potassium channels are included (Soveri et al., 2019). Even though the use of oxaliplatin in chemotherapy, a treatment for colon cancer, may cause toxicities, it continues to be used because it reduces the rate of cancer metastasis (Drott et al., 2018). Neurotoxic side effects have been observed to occur in approximately 85% of patients after this treatment (Cheng et al., 2023). Oxaliplatin has neurotoxic effects such as sensitivity to cold, lethargy, neuropathic pain and muscle cramps, lethargy, rare motor and autonomic damage, and sensory peripheral neuropathy, that is, loss of sensation, which are side effects (Cheng et al., 2023; Drott et al., 2018). According to a study conducted in 2018 on the neurotoxicity effect of oxaliplatin treatment

in patients with colorectal cancer, which includes the colon part of the intestine, neurotoxic effects in individuals were reported (Drott et al., 2018). The patients in the study had stage II and III colorectal cancer and were receiving chemotherapy treatment with oxaliplatin after surgery. Patients experienced serious sensitivity to cold in their hands, feet, and face, found the coldness of the food uncomfortable even when consuming it, and in addition, felt tingling in the body. These neurotoxic effects also negatively affected people's social lives (Drott et al., 2018). Efforts to reduce neurotoxicity include changing the dose over time, changing the route of administration, and rearranging the drugs in combination (Cheng et al., 2023). In addition to these studies, the use of calcium and magnesium is also used for treatment purposes that reduce neurotoxicity (Zhang et al., 2020).

Some neuropathic symptoms may occur in colon cancer patients years after chemotherapy treatment is stopped. According to another study conducted in 2018 to examine the occurrence of neuropathy in colorectal (cancer formation in the colon or rectum area) cancer patients who received chemotherapy with oxaliplatin, years after the treatment ended, the data of 144 patients using CAPOX or FOLFOX were examined. (Soveri et al., 2019).The majority of these patients were stage III. According to the data obtained, no major difference was found in terms of change in neuropathy between those using the CAPOX or FOLFOX drug regimen, and no difference in their quality of life was detected. Long-term side effects include numbness and tingling in the hands and feet (Soveri et al., 2019).

5-FU, a chemotherapy agent, can also cause serious toxic effects in cancer patients. While it generally causes symptoms such as fatigue, nausea, vomiting and diarrhea, it also causes toxicities such as leukopenia, neutropenia, anemia, and neuropathy. It was observed that the addition of irinotecan and oxaliplatin to 5-FU increased its benefits and, increased its toxic effects (Vodenkova et al., 2020). It has been observed that gastrointestinal and mucositis toxicities increase in patients with long-term treatments because of the use of 5-FU. To interpret the toxicity that men and women are exposed to by 5-FU in colon cancer, some studies have shown that more severe hematologic toxicities may occur in women (Chansky et al., 2005). According to another study on this subject, side effects such as stomatitis, leukopenia, alopecia, and gastrointestinal problems, were more severe in women than in men. However, it was stated that more detailed research is still needed (Chansky et al., 2005).

The intestinal microbiota is composed of many microorganisms, where nutrients are absorbed, metabolites are synthesized, and tissue development occurs through the growth of epithelial cells in the intestine (Mohamed et al., 2021). Intestinal microflora varies from person to person depending on their gender, diet, medications used, emotions they are exposed to and immune system (Zahrani et al., 2019). The intestinal microbiota, which plays a role in the formation of side effects in cancer patients, has an important role in regulating the effectiveness of drugs in chemotherapy treatment and the formation of toxicity (Chrysostomou et al., 2023). Although research in this field is still ongoing, important information is available. For example, *E. coli*

bacteria, which is also found in the colon part of the intestine, plays a critical role in the metabolism of drugs. These bacteria can alter the metabolization of 5-FU, thus altering the effectiveness and toxicity of the drug (Lehouritis et al., 2015). *F. nucleatum*, one of the mucosal pathobionts among microorganisms living in the stomach, pancreas, and small intestine, plays a role in the immune system. However, as these bacteria increase, resistance to 5-FU and oxaliplatin chemotherapy drugs used against colon cancer cells increases and the risk of toxicity increases (Chrysostomou et al., 2023). Microbial β-glucuronidases found in the intestine are involved in the removal of chemicals from the body (Pollet et al., 2017). During the metabolism of the chemotherapy drugs irinotecan by these microbes, damage occurs in the intestine and toxicity occurs. This can cause severe diarrhea. Therefore, changes that may occur in the intestinal microbiota significantly affect the responses and toxicities of cancer patients to chemotherapy drugs (Chrysostomou et al., 2023).

It is known that changes in the intestinal microbiota may cause toxic effects during chemotherapy, and research also shows that it plays a role in the development of cancer (Mohamed et al., 2021). It has been observed that dysbiosis of the intestinal microbiota, that is, disruption of intestinal homeostasis, plays a role in the onset of colorectal cancer (Kosumi et al., 2018). For example, cancer formation may begin when some bacterial species disrupt the signaling pathways of colon cells or some bacteria may cause DNA damage by producing carcinogenic toxins, which may initiate cancer. It has been observed that *Bacteroides fragilis* bacteria in the intestinal microbiota promote the onset of colon

cancer by producing genotoxic toxins (Sears et al., 2014). Studies have shown that antibiotic use may have effects on colon cancer (Mohamed et al., 2021). Antibiotics are drugs that have a lethal effect on bacteria (Gao et al., 2020). It has been observed that antibiotic use disrupts the density of the intestinal microbiota, which varies from person to person, and changes its diversity in the long and short term (Mohamed et al., 2021). In addition, as a result of antibiotic use during chemotherapy, chronic inflammation, that is, long-term inflammation in the body, and toxicity may occur due to the decrease in the body's immunity (Gao et al., 2020). It has been shown that disruption of intestinal hemostasis because of the use of antibiotics may play a role in the development of diseases other than cancer (Mohamed et al., 2021).

In addition, the immune T cells also play a role in cancer development. Cancer treatments can be performed using immune checkpoint inhibitors. In immunotherapy, cell checkpoint molecules such as PD-1 and PD-L1, which are target cells, are stopped from working. In this way, immune cells are enabled to destroy cancer cells. Cytotoxic drugs 5-FU and oxaliplatin can be used in this treatment because they have immunological properties. These properties appear to trigger immune system activation so that the immune system begins to destroy cancer cells (Dosset et al., 2018). Although this immunotherapy method provides positive results for cancer, inflammatory toxicities may occur as a result. In immunotherapy, organs may be negatively affected and even organ death may occur due to overstimulation of the immune system. The skin and liver are affected by the common inflammatory toxicities that occur with this

immunotherapy (Dougan, 2020). Some toxicities were observed in phase I studies of embrolizumab and nivolumab immunotherapy drugs, which are PD-1 blockers used in colorectal colon cancer. These were symptoms such as fatigue, pain, respiratory system disorder, cough and shortness of breath, thrombocytopenia, and leukopenia (Wrobel & Ahmed, 2019). In phase II studies involving the treatment of 74 patients with the immunotherapy drug Nivolumab, a PD-1 inhibitor, it was shown to be a therapeutic drug for colorectal colon cancer. While common toxicities include fatigue and diarrhea, uncommon side effects include colitis, hepatitis, and adrenal insufficiency (Wrobel & Ahmed, 2019). Another immunotherapy drug used in colorectal cancer is ipilimumab, a CTLA-4 inhibitor that is associated with T lymphocytes. With the CTLA-4 inhibitor, the immune system blocks the tumor and causes it to shrink (Breakstone, 2021). This drug has been seen to be more effective when combined with the drug nivolumab. Studies have shown that in patients who received this treatment method, the tumor shrank and disappeared over time in areas where it had metastasized, such as in the lung (Igaue et al., 2022). The toxicities reported by patients who received this treatment were as follows: diarrhea, itching, hypothyroidism with endocrine toxicity, pyrexia, skin rash, and 1st or 2nd-degree toxicity in the kidneys and lungs (André et al., 2022).

4.2. Stomach Cancer

The stomach, located in the human digestive system, consists of a muscular structure. It plays a role in the digestion of food by secreting stomach acid (Hunt et al., 2015). Stomach cancer occurs with the

uncontrolled proliferation of cells on the inner surface of the stomach. It is one of the most common cancers in the world and has a high mortality rate (Alim et al., 2020). The incidence and mortality rate of stomach cancer generally begin to increase by middle age and its incidence is highest in people after the age of 60 (Ilic & Ilic, 2022; Nagini, 2012). East Asia and Eastern Europe are the leading places for stomach cancer (Nagini, 2012). Environmental factors to which the person is exposed play an important role in the development of stomach cancer. These risk factors include having a *Helicobacter pylori* infection, consuming excessively salty foods, obesity, radiation, tobacco and alcohol use, and an unhealthy diet by not eating fruits and vegetables. Additionally, those with a family history of this disease are at hereditary risk (Ilic & Ilic, 2022). Patients with stomach cancer may show non-specific symptoms, including common indigestion, constipation, nausea, and diarrhea. As a result of the symptoms, the diagnosis of stomach cancer is determined mostly by endoscopic biopsy (Alim et al., 2020).

4.2.1. Stomach Cancer Mechanism

Since stomach cancer is a type of cancer arising from epithelial cells, it is referred to as adenocarcinoma. Stomach cancer can start anywhere between the gastroesophageal junction at the top of the stomach and the pyloric part of the stomach that connects to the intestine at the bottom of the stomach, including the starting and ending points of the stomach (Nagini, 2012). One of the reasons for the development of stomach cancer can be explained by Correa's Cascade

model. According to the model, the first chronic gastritis. It is caused by long-term inflammation of the healthy cells that form the inner surface of the stomach (Correa, 1992). The cause of this inflammation is usually *H. pylori* bacteria. Subsequently, the inner surface of the stomach is damaged due to this inflammation. Thus, the organ cannot function adequately. Then, the intestinal metaplasia stage occurs, in which the cells in the stomach begin to resemble intestinal cells. In the next stage, dysplasia, abnormal changes that pose the risk of turning into cancer begin to occur. As a result of the rapid proliferation of these abnormal cells in the stomach, carcinoma, that is, stomach cancer, occurs (Battista et al., 2021). According to the research, the *H. pylori* bacteria, which is infected in most people and can cause the mentioned processes, is the biggest factor in the formation of stomach cancer. However, other factors that can cause stomach cancer cannot be ignored (Gullo et al., 2020).

Mucins, the mucus layer on the inner surface of the stomach, protect the stomach against harmful substances (Shankar et al., 1994). Abnormalities in these mucins are observed in patients with stomach cancer. It has been observed that the *MUC2* gene is expressed in these cancer patients (Battista et al., 2021). It has been observed that because of long-term exposure of the stomach to inflammation, the mucosa layer becomes damaged and thinned, digestive enzymes cannot produce enough and lesions that can turn into cancer may increase (Battista et al., 2021).

Intestinal metaplasia has an important role in stomach cancer. Here, stomach epithelial cells turn into intestinal epithelial cells and

carry the risk of cancer (Battista et al., 2021). This lesion can be seen in only one part of the stomach or multiple parts (Jencks et al., 2018). The resulting tissues of the lesion are divided into two: complete type I and incomplete type II (Reis et al., 1999). In type I, the stomach resembles the goblet cells of the intestine, while in type II, structures like the colon part of the intestine are seen in the stomach. These lesions occurring in the stomach can be seen in Figure 4 (Jencks et al., 2018). It is known that *CDX* genes play a role in the formation of these bowel-like lesions (Battista et al., 2021).

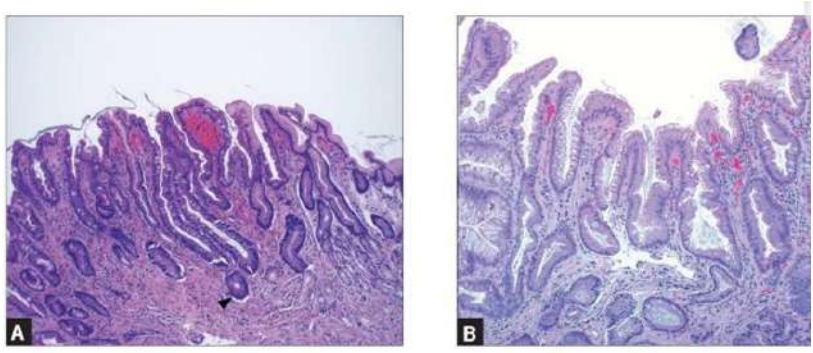

Figure 4. Intestinal metaplasia is seen in the stomach. The figure shows an example of intestinal metaplasia seen in the stomach. Figure 4 A is also complete intestinal metaplasia, where the formation of goblet cells and mucin vacuoles is observed. Figure 4B Incomplete intestinal metaplasia. Here, irregular mucin droplets and columnar intermediate cells are seen (Jencks et al., 2018).

After the intestinal metaplasia stage, gastric dysplasia, which is the cancerous stage, occurs. At this stage, cancer may arise from a new lesion or existing polyps in the stomach (Battista et al., 2021). These polyps can be grouped as benign, hyperplastic, or juvenile. While in this stage, neoplastic changes occur in the epithelial cells of the stomach (Gullo et al., 2020).

Known as polyps, these stomach adenomas are abnormal tissue growths. They are distinguished from each other according to the part of the stomach where they form (Gullo et al., 2020). Some of the adenomas that form in the stomach may remain as adenomas. However, adenomas can progress towards carcinoma because of exposure to certain risk factors (Okamoto et al., 2021). According to studies conducted on risk factors that increase stomach cancer, the biggest risk factors are *H. pylori* infection and smoking or having smoked before. Other risk factors included alcohol use, being overweight according to body mass index, consuming pickled vegetables, and consuming high-salt foods. It has been observed that *H. pylori* bacteria here constitute a risk factor for cancer cause of disrupting the protein activities of stomach epithelial cells (Poorolajal et al., 2020). In addition, consumption of too much salty food causes the proliferation of these bacteria and gastritis. Thus, it is seen that damage to the stomach is an important risk factor in the progression of cancer (Nagini, 2012).

On the other hand, it is known that antioxidants taken from food are beneficial to prevent stomach cancer (Nagini, 2012). Especially, studies have shown that the risk of cancer is significantly reduced

hereby regular consumption of fruits and vegetables (Poorolajal et al., 2020).

4.2.2. Stomach Cancer Treatment with Chemotherapy

Stomach cancer can be detected incidentally during check-ups, as small lesions do not cause obvious symptoms in patients. After the disease is detected, it is treated according to its stage. However, patients are usually diagnosed late because they show obvious symptoms in advanced stages (Delaunoit, 2011). If advanced-stage patients with stomach cancer are not treated with chemotherapy, their survival rates are low (Rivera et al., 2007). Surgery, which is one of the treatment methods, is not suitable for every cancer patient. Another treatment methods, the endoscopic mucosal resection can be performed when the cancer is in the mucosa and submucosa of the stomach, that is, in the early stage (Delaunoit, 2011). Endoscopic mucosal resection is the process of removing abnormal cells formed on these surfaces with the help of an endoscope. There are cases where this procedure can be curative without the need for surgery The disease may not be eliminated by removing the cancerous tissue because of the surgical procedure (Ma & Bourke, 2016).

The adjuvant chemotherapy treatment is to prevent the cancer from reoccurring after surgery(Delaunoit, 2011). The time to start adjuvant chemotherapy and the drug combinations used may vary between countries (Maehara et al., 2001). Thanks to phase III studies show that the use of S-1 (tegafur, gimeracil and oteracil potassium) adjuvant chemotherapy, that is, orally taken combined chemotherapy

drugs, improvement was observed in advanced-stage gastric cancer patients with D2 lymph node dissection. The components of the drug S-1, tegafur is the prodrug of 5-FU, and gimeracil acts as an enzyme inhibitor that breaks down 5-FU, and oterasil prevents the digestion of 5-FU. Phase II studies have shown that even the use of S-1 alone increases the chances of survival in patients with stomach cancer. Thus, S-1 has become an important treatment method in adjuvant chemotherapy (Kilic et al., 2016; Kobayakawa & Kojima, 2011). Palliative chemotherapy methods are also applied to relieve the symptoms experienced by stomach cancer patients and increase their survival time (Delaunoit, 2011). With this palliative chemotherapy, improvements can occasionally occur in patients with incurable stomach cancer. It is generally used in advanced cancer patients to control disturbing symptoms such as pain and nausea and to increase the quality of life (Merchant et al., 2021). Palliative chemotherapy is used to treat cancer cells that have spread regionally to the peritoneal part of the stomach. Direct application of cytotoxic chemotherapy drugs into the peritoneal cavity is also used. In this way, exposure to systemic toxicity is reduced (Koemans et al., 2019). However, if tumors occurring in the stomach spread proximally, that is, in the main part of the stomach, the survival rates of patients are low despite treatment. The prognosis of cancer formation in the distal region, close to the exit part of the stomach, is better and patients have a higher chance of survival. Stomach cancer patients are treated using drugs such as 5-FU, cisplatin and docetaxel regimen, 5-FU, irinotecan, leucovorin drug regimen, pirubicin, cisplatin, 5-FU drug regimen (Aznab et al., 2017). Since

cisplatin has a high success rate in chemotherapy treatment, it is frequently used in drug combinations (Rivera et al., 2007).

4.2.3 Chemotherapy Toxicity Effects in Stomach Cancer

Chemotherapy is one of the treatment methods for stomach cancer that causes toxicities in patients (Palmela et al., 2017). Because the use of these drugs increases the chances of survival of cancer patients, they continue to be used despite toxicities. These toxicities caused by chemotherapy drugs can be direct or indirect (Was et al., 2022).

Sarcopenic obesity is a condition in which patients' muscle mass decreases and their fat tissue increases. Studies have shown that patients with this condition experience more toxicity and have lower survival rates than other patients when receiving neoadjuvant chemotherapy for stomach cancer. On the other hand, it has been observed that patients who do not respond to this neoadjuvant chemotherapy treatment also experience decreases in muscle and fat tissue (Palmela et al., 2017). While cancer patients with sarcopenia experience more toxicities, they may also face serious complications such as infection. This causes dose reduction or discontinuation of chemotherapy treatment (Wu et al., 2020).

It has been observed that the addition of docetaxel to the drug combination of cisplatin and 5-FU used in the treatment of stomach cancer increases the survival rate in patients. However, there are cases where it causes toxicities, especially in individuals over the age of 65 (Meza-Junco et al., 2011). This chemotherapy drug combination

appears to cause the most common hematological toxicities in general cancer patients. Among these, the rates of neutropenia and anemia toxicities are high (Ajani, 2008). Studies show that the use of docetaxel can directly cause neurotoxicity. This drug is a semi-synthetic in the taxane drug group. Allergic reactions occur during the dissolution of the drug. In line with toxicity research studies, it has been observed that taxane drugs affect neural transport in axons, so neurons cannot function (Was et al., 2022). By combining docetaxel, which is used during cancer treatment, with doxorubicin and cyclophosphamide, some changes occurred in the microglia cells in patients. It has been observed that these microglia cells undergo morphological changes. As neuronal stem cells are disrupted by this change, neurogenesis, the process of new nerve formation in the hippocampus, is prevented (Was et al., 2022).

One of the chemotherapy regimens used in patients with gastroesophageal adenocarcinoma was a drug combination containing cisplatin, 5-FU, and epirubicin. However, thanks to phase III studies, it was seen that recovery was achieved only with cisplatin and 5-FU without the use of epirubicin, and that epirubicin caused toxicity. For this reason, epirubicin is no longer preferred in perioperative regimens (Joshi & Badgwell, 2021). Epirubicin prevents the topoisomerase II enzyme from binding to DNA, causing the DNA knots to break. Cancer cells affected by epirubicin are damaged and die. But also, it has serious toxic effects on healthy cells. These are as the toxicity, which can lead to heart failure, and nephrotoxicity, which results in severe kidney diseases, and hepatoxicity (Owumi et al., 2023). In addition, studies

have shown that the use of epirubicin causes changes in the morphology of erythrocytes, and that the oxygen in the vessels is affected by the deterioration of the form of red blood cells, which triggers tissue damage. Since epirubicin, an anthracycline antibiotic has toxic effects at the cellular level, it is used by paying attention to the maximum tolerated dose in patients (Petit et al., 2020). Mitomycin c, an antitumor antibiotic, is also used in the treatment of stomach cancer. The common toxicity of this drug is on the bone marrow. Therefore, attention is paid to toxicities by limiting the doses of mitomycin c given to patients (De Vivo et al., 2000).

According to a study conducted to examine whether toxicities occurring in stomach cancer patients were related to age, chemotherapy-related toxicities were high in individuals over the age of 65. One of the reasons for this is the changes in the pharmacokinetics of drugs due to aging. For example, in these individuals, the body will be exposed to this drug for a long time, as the rate of elimination of drugs such as epirubicin, used in the treatment of stomach cancer, from the blood will slow down (Slagter et al., 2020).

In a phase III study, it was observed that elderly patients with esophagogastric cancer could not tolerate the drug combination of epirubicin, oxaliplatin and capecitabine due to toxicities, so treatment was continued with the drug combination of oxaliplatin and capecitabine, and it was observed that less toxicity occurred in elderly patients treated with low doses (Slagter et al., 2020).

Intraperitoneal administration of paclitaxel, that is, directly into the abdominal cavity, is also included in the treatment of stomach

cancer (Kobayashi et al., 2024; Sugarbaker, 2021). By administering the drug directly, it increases its effectiveness as it does not enter systemic circulation. In a phase II study, the treatment of stomach cancer patients with peritoneal metastasis with S-1, cisplatin and paclitaxel with chemotherapy drugs were examined. Toxicities that occurred in patients included anorexia, taste disturbance, vomiting, diarrhea, anemia, abdominal pain, neutropenia, and leukopenia. It continues to be used since the toxicities that occur are not fatal because it increases the 1-year survival rates of patients in studies (Kobayashi et al., 2024). Among the toxicities that occur, neutropenia is generally dose-limiting. When paclitaxel is given to patients intravenously with cisplatin rather than directly, the normal functioning of the bone marrow is blocked and toxicity occurs (Sugarbaker, 2021).

Chemotherapy drugs used in the treatment of stomach cancer can cause cardiotoxicity due to arrhythmia and pulmonary hypertension. Long-term use of 5-FU, the most well-known among these, can trigger coronary spasms in the heart and cause toxicities such as heart attack. Another drug that may cause cardiovascular side effects is cisplatin. It can generally have effects such as high blood pressure and thickening of the heart vessels (Radulescu et al., 2021). Another drug group in which cardiotoxicity may occur is chemotherapy treatment using immune checkpoint inhibitors (Radulescu et al., 2021). Among these drugs, nivolumab and pembrolizumab are used as immunosuppressants in the treatment of gastric cancer. The functioning of PD-1 is blocked by anti-PD-1anti-PD-1 agents in patients using the drug. Thanks to this inhibition, the immune system does not allow cancer cells to survive

(Dosset et al., 2018; Radulescu et al., 2021). Studies show that myocardia, which is a cardiotoxicity, has been observed in patients with the use of immune trigger drugs (Radulescu et al., 2021). Cardiotoxicity that occurs can continue after treatment and leave permanent scars for life. However, sometimes these symptoms may be temporary after treatment (Curigliano et al., 2016).

There are chemotherapy drug regimens that can produce high toxicity, so research and phase studies continue to look for new drug combinations with less toxicity. A phase III study involving 583 patients with advanced gastric cancer showed that the use of S-1 and oxaliplatin as a chemotherapy regimen did not produce worse toxicity than the combination of 5-FU, leucovorin, and oxaliplatin. Therefore, it has been an effective method for the treatment of neutrocytopenia, in which almost the same degree of hematological toxicity, was observed in both groups. Similar rates of vomiting and nausea were observed in other toxicities (Yu et al., 2022).

4.3. Liver Cancer

The liver, which is a vital organ, has a variety of purposes in our body. The functions of the liver include metabolizing, digesting and excreting substances taken into the body. The liver secretes bile, which helps these processes. It also plays a role in the process called the reticuloendothelial system for the body's immune system. In the reticuloendothelial system of the liver, microorganisms that are foreign to the body are cleared from the blood with the help of phagocytosis (Hoekstra et al., 2013).

The liver, one of the major organs of our body that renews itself frequently resulting increased possibility of cancer occurring there (Yang et al., 2019). Liver cancer is one of the most common deadly cancers in the world (Donne & Lujambio, 2023). Cancer occurring in the liver, hepatocellular carcinoma (HCC), and intrahepatic cholangiocarcinoma (ICC), are the strongest common primary cancer types as the first place it appears in patients (Orcutt & Anaya, 2018). Excepting these liver cancer classifications, metastatic liver cancer can include (Bakrania et al., 2023). The presence of certain risk factors is often taken into consideration in the emergence of liver cancer, which is especially more encountered in developing countries (Anwanwan et al., 2020). Examples of these potential hazards that play a role in the development of liver cancer are chronic inflammation disease caused by the hepatitis B virus and hepatitis C virus, excessive fatty liver, diseases such as obesity and diabetes, and environmental factors such as heavy smoking and using alcohol (Bakrania et al., 2023; Srivatanakul et al., 2004). On the other hand, according to research, some foods suppress the mechanisms that cause the development of liver cancer. For example, thanks to the compounds found in fruits and vegetables, it can prevent cancer formation by stimulating systems such as antitumor and anti-inflammatory (Anwanwan et al., 2020).

Surgical treatment rates are generally low in the treatment of patients who develop liver cancer. For providing suitable conditions for surgical treatment, the disease must be in the early stages and the patients must not have cirrhosis in order for the liver to continue to renew itself (Anwanwan et al., 2020). Cirrhosis is a condition in which

normal tissues in the liver become abnormal and become chronically damaged due to reasons such as excessive alcohol consumption and hepatitis C infection (Poordad, 2015).

4.3.1. Liver Cancer Mechanism

While the majority of liver cancer patients have HCC, which originates from hepatocytes, the main cells of the liver, less common types include cholangiocarcinoma, which affects the liver bile ducts, and other types. Although the liver is constantly exposed to toxins, it is highly tolerant and prevents the immune system from reacting unnecessarily (Yang et al., 2019). Thanks to this feature of the liver, it prevents tissue rejection by helping the body accept the liver in liver transplant surgeries. In addition, thanks to the self-defense immune system of the liver, the formation of cancerous cells is tried to be prevented by the liver. Hepatitis viruses and alcohol consumption seriously disrupt the liver's unique immune system (Yang et al., 2019). Liver damage caused by viral infections such as hepatitis B and C continues chronically all life. This process has led to the result of the liver continues to create structures such as glycoprotein and collagen to heal injured tissues, and after a while, these extracellular matrices replace liver cells. As these fibrotic structures replace liver cells, they cause permanent, irreversible cellular damage in the liver over time (S. Sun et al., 2022). Because of this process that causes chronic inflammation, liver cells cannot fulfill their function and become susceptible to mutations. Cancer occurs with the accumulation of these mutations (Yang et al., 2019). In addition, it is observed that damage to

liver cells due to obesity causes inflammation, which increases the production of cytokines and adipokines, leading to liver cancer. (B. Sun & Karin, 2012). In addition, as inflammation continues, collagen accumulation in the liver increases, causing fibrosis, which is a hardening of the connective tissue, and cirrhosis, which is a loss of tissue function. Due to cirrhosis, liver failure or re-cancer risk may occur (Li et al., 2021). In studies conducted on patients with liver cancer, it has been observed that chromosomal abnormalities and gene deletions occur and also, viral infections may cause genetic mutations by disrupting telomerase enzyme activities, therefore it is thought that current treatments should be improved (Feng et al., 2020; Rajapaksha, 2022).

In addition to primary cancer occurring in the liver, it is also frequently observed in patients that cancer reaches the liver secondarily, that is, through metastasis. The interaction of the liver with other organs resulting from its anatomical structure makes this situation even easier (Li et al., 2021).

4.3.2. Liver Cancer Treatment with Chemotherapy

As a consequence of examinations carried out on patients with liver cancer, a specific treatment method is decided according to the stage and course of the disease and the symptoms shown by the patient. There are multiple treatment methods used for liver cancer. The most used of these are surgically operating on the patient's liver or organ transplantation, administering radiation-containing rays to cancer cells, and administering drug therapy with chemotherapy (Feng et al., 2020).

Treat cancer patients' chemotherapy is a treatment method that can often cause toxicity in patients if not used correctly therefore, studies show that depending on the type of cancer, chemotherapy drugs can have better effects when given in combination rather than alone (Asghar & Meyer, 2012). It is used with cytotoxic chemotherapy in the treatment of HCC, the most common type of liver cancer. Although the survival rates have increased in patients with normal liver function with this treatment, patients with severe liver damage may not benefit from the drugs as they cannot be tolerated by the liver (Rajapaksha, 2022). The fact that this type of cancer has a very complex system reduces the effectiveness of its treatments (Li et al., 2021).

Chemotherapeutic drugs are given to patients with HCC alone or in combination, for example, the drug regimen consisting of 5-FU, leucovorin and oxaliplatin is frequently used in patients. (Rajapaksha, 2022). Like other chemotherapeutic drug regimen, PIAF, consisting of cisplatin, interferon alpha-2b, doxorubicin and 5-FU, is used therapeutically (Feng et al., 2020). As well as doxorubicin is a chemotherapy drug that can be administered directly to the liver, the tumor tissue, during cancer treatment (Meng et al., 2012). Other one chemotherapy drug, floxuridine (FUDR), is more effective when given directly to the liver. This drug is effective in primary liver cancers as well as cancers that metastasize to the liver (Jarnagin et al., 2009). The one of first chemotherapy drugs called gemcitabine was used in the treatment of ICC in the biliary tract. In the following years, more effective drug combinations containing gemcitabine, fluoropyrimidine and platinum began to be used XELOX, a combination of capecitabine

and oxaliplatin, and GEMOX, a combination of gemcitabine and oxaliplatin, are used in chemotherapy treatment in cholangiocarcinoma patients. According to a phase III study, XELOX, one of these drugs, was generally found to be more effective in patients (Feng et al., 2020). Sorafenib, to be accepted in 2016, is a systemic chemotherapy drug used in the treatment of HCC patients. As another drug, gemcitabine can be used in patients alone with advanced liver cancer when deemed necessary and it can also be given to patients in combination with drugs such as cisplatin (Kim et al., 2017).

Anticancer chemotherapy drugs used in liver cancer treatment may become resistant and ineffective in cases such as HCC. Encountered resistance situations are classified by certain systems such as multidrug overcoming classification (MOC). One of the reasons for resistance in cancer drugs occurs due to the decrease in the function of carrier proteins in the SLC family in the cell membrane (Marin et al., 2018). In the classification known as MOC-1a, carrier proteins with reduced function are unable to take anticancer drugs into the cell. As examples of this situation, irinotecan, methotrexate, docetaxel, and cisplatin drugs may decrease their effects on the cell as chemotherapeutics according to the MOC-1a classification. In addition, drugs such as cisplatin, which directly change the structure of DNA used in chemotherapy treatment, cause HCC cancer cells to develop resistance to drugs due to the overproduction of proteins such as *ERCC1* (Marin et al., 2018).

4.3.3. Chemotherapy Toxicity Effects in Liver Cancer

Toxicities are encountered in chemotherapy, which is a curative treatment frequently used in patients with liver cancer compared to other treatment methods. As the tolerability of the chemotherapy drug method gradually decreases in patients with liver diseases, the risk of toxicity increases (Kim et al., 2017). One other reason for toxicity is that the chemotherapy drugs used today have low specificity and can also damage other non-cancerous cells (Meng et al., 2012).

Doxorubicin, obtained from the *Streptomyces peucetius* bacterium used in cancer treatments, is used to treat liver cancer by giving it systemically or directly through the veins leading to the liver (Tam, 2013). Unfortunately, the chemotherapy drug doxorubicin, which has a healing effect and is frequently used in liver cancer treatment, can be quite toxic. Doxorubicin prevents the growth of cells by reaching the nucleus of the cells and binding them to chromosomal DNA. Thanks to this binding, it blocks the growth and proliferation of cells. Unfortunately, it also causes toxicity by reaching healthy cells and preventing them from multiplying, which can seriously stop the use of the drug and thus the course of liver cancer treatment (Meng et al., 2012). As another side effect, the damage caused by doxorubicin to the heart is significant enough to stop the treatment. However, it has been observed that if the drug is given to patients directly through the liver artery, it increases its effectiveness on cancer cells and reduces the risk of toxicity on other cells (Tam, 2013). According to studies conducted in patients using doxorubicin, toxicities are divided into certain groups. First, the most common acute side effects included nausea, hair loss,

and decreased blood cell production, which increased the risk of infection. According to another grouping, there were serious side effects that developed over time and continued by becoming chronic. For example, cardiotoxicities resulting from the use of doxorubicin for the treatment of liver cancer were the most common side effects of this group. One of the many reasons behind the occurrence of these side effects is that the drug produces free radicals, which can be toxic to human health (Tam, 2013). In a study conducted to improve treatment with doxorubicin, that is, to reduce toxicity rates, pegylated liposomal doxorubicin (PLD) was developed. This liposome-coated drug remains in the body for a longer time without being broken down, thus reducing the toxicities caused by the rapid breakdown of the drug. However, in line with the phase II cancer studies, it was seen that this treatment method alone was not sufficient to eliminate the tumor and needed to be improved (Kim et al., 2017).

While direct injection of chemotherapy drugs into the liver aims to prevent cancerous tissues from being fed through the vessels, some toxicities may occur. The FUDR chemotherapy drug generally used in this form of treatment is intended to reduce systemic toxicity by creating exposure only to hepatic tumors in the liver (Jarnagin et al., 2009). In line with studies conducted on patients, toxicities such as sudden increases in liver enzyme serum bilirubin levels, diarrhea, migraine, tachycardia, and abdominal pain have been observed because of this treatment (Jarnagin et al., 2009). Side effects on liver enzyme values may occur as a result of giving FUDR in combination with dexamethasone, oxaliplatin and irinotecan drugs. As a result of the

examination of the patients, an increase in the level of liver AST, high bilirubin level, and increases in the level of alkaline phosphatase, which is involved in bile production, were observed. According to these increased enzyme values, a dose adjustment containing FUDR must be made again (Power & Kemeny, 2009).

As another drug combination, GEMOX affects advanced liver cancer cells. Although it is a treatment method that shrinks tumor cells and prolongs survival, toxicities occur in some patients. Patients generally experience serious side effects such as neurotoxicity and neutropenia, which cause dose adjustments (Grazie et al., 2017). Phase studies show that the treatment method is more successful, as GEMOX is well tolerated in patients with non-alcoholic cirrhosis and no renal toxicity is observed. According to another study using GEMOX, hematological toxicity was observed to occur commonly in patients (Louafi et al., 2007). Studies on XELOX, which is also an oxaliplatin-containing drug regimen, show that it contains acceptable toxicities for HCC, just like GEMOX. According to studies conducted with samples taken from patients, toxicities include increased liver enzyme values such as bilirubin, thrombocytopenia, and neurotoxicity. Severe neuropathy is often a treatment-limiting side effect of this drug (Boige et al., 2007).

The FOLFOX drug combination, which is actively used in liver cancer treatment, can be administered directly into the veins leading to the liver. It has been observed that systemic toxicities are reduced by direct injection, preventing the drug from spreading throughout the body. According to studies conducted on patients, some of the reasons

for toxicity were bleeding in the liver vessels of the patients and liver failure. Toxicities such as thrombocytopenia, vomiting, fever, and immune system impairment may occur in patients after treatment (Wang et al., 2022). According to the phase studies conducted on patients with liver cancer using the PIAF drug combination, it was determined that patients without previous chronic liver diseases did not show resistance to chemotherapy and gave better results in terms of hepatoxicity (Kaseb et al., 2013). In another phase II study, the toxicities that usually occur cause of administering drugs frequently used for HCC treatment to individual patients were investigated. According to this study, when doxorubicin drugs were given to individual patients, it caused toxicities such as anorexia, alopecia, myelosuppression, 5 FU drug generally mucositis and neutropenia, and capecitabine hand and foot syndrome. Phase II studies on another combination drug treatment, gemcitabine, and cisplatin, show that this method gave similar results to other liver chemotherapy treatment combinations (Eatrides et al., 2017). According to another phase II study conducted with gemcitabine and cisplatin, toxicities such as anemia, neutropenia and thrombocytopenia occurred in patients given the combination. After another phase study in which the doses of the drug were changed, it is seen as a drug combination open to trial in patients with mild liver failure and in patients who cannot be treated with sorafenib, as the combination is more effective in some patients and less effective in some patients (Kim et al., 2017).

The tyrosine kinase inhibitor sorafenib, which has a mechanism of inhibiting vascular endothelial growth factor, is used to treat liver

cancer. It is a clinically approved treatment that prolongs life, and it was given to patients in a phase study combined with chemotherapy drugs. In a phase II study in which it was combined with doxorubicin, comparisons made in patients found that sorafenib was more beneficial when given alone. In a phase III study conducted with the same drugs, it was determined that there was no improvement in the survival of the patients and toxicities occurred more than in normal chemotherapy treatment (Eatrides et al., 2017). Phase II clinical studies conducted with the anti-EGFR drug cetuximab, which blocks the growth factors of cancer cells, and the combination of cetuximab and the chemotherapy drug oxaliplatin, showed that it is a promising treatment method with a high disease control rate, but it cannot yet extend life as much as other combinations, but it may be a treatment method that needs further study (Eatrides et al., 2017).

Hormonal treatments were among the studies conducted for liver cancer. Studies have shown that the presence of hormonal receptors in this type of cancer has led to the investigation of this treatment method. In line with the studies conducted, the connection between drugs such as tamoxifen, megestrol, and octreotide and liver tumors were investigated, and since they were not effective on the tumor alone, they were combined with chemotherapy drugs such as doxorubicin. However, because of the phase studies, the hormonal treatment is not used because these combinations are not effective enough (Kim et al., 2017).

4.4. Kidney Cancer

The function of the kidneys, which are one of the most important organs of vital value for the body, is to take part in the excretion of metabolic waste from the body. (Finco, 1997). Kidneys, it maintains the fluid and electrolyte (sodium chloride) balance required for the body by filtering the blood and subsequently producing urine. Kidneys, which are controlled systemically and locally by the body, play a critical role in ensuring homeostasis. The fluid filtered by the kidney is reabsorbed through the renal canals, providing hemostasis, and preventing excessive fluid and salt loss. The adenosine molecule in the kidneys plays an important role in regulating these kidney functions, for example, it regulates functions such as Glomerular filtration rate (GFR), that is, the amount of urine produced per minute, salt absorption, and blood flow rate. (Vallon et al., 2006). Loss of function may occur due to deterioration in these functions, which is why azotemia, that is, high amounts of urea in the blood, occurs. Consequently, serious kidney diseases such as kidney failure may occur, which reduce the person's quality of life (Finco, 1997). Kidney cancer is one of the serious cancers that increases over time and may be caused by some specific factors (Linehan & Zbar, 2004). The most common type of cancer seen in the kidneys is known as renal cell carcinoma (RCC), also known as Gradwitz tumor. Most of these kidney tumors can be easily visualized and can be detected and treated quickly at the first stage (Hancock & Georgiades, 2016). There are some risk factors for cancer in the kidneys, the most common of which are hereditary diseases, such as having Von Hippel Lindau Syndrome, having chronic kidney diseases,

being over 65 years old, being overweight, having high blood pressure that is difficult to control, and is heavy smoking (Hancock & Georgiades, 2016; Linehan & Zbar, 2004). Recent studies on kidney cancer, which may not show symptoms in the early stages, show that its mortality rate is dangerous when it metastasizes and spreads throughout the body (Nasir et al., 2022).

4.4.1. Kidney Cancer Mechanism

Some diseases increase the risk of cancer in the kidneys and other organs, for example, patients with Von Hippel Lindau Syndrome have the risk of benign or malignant tumors in various organs such as kidneys, pancreas, adrenal glands, and eyes. When this disease occurs in the kidneys, it is called clear cell kidney cancer (Linehan & Zbar, 2004). This disease occurs owing to some mutations in the *VHL* tumor suppressor gene and is involved in the cell cycle and angiogenesis processes (Pascual & Borque, 2008). Kidney lesions of people with this mutation are impaired due to the mutation in the *VHL* gene, and an increase occurs because this gene cannot regulate the level of the HIF protein, which is its main function. The increase in HIF protein causes irregular cell growth, that is, cancer, by increasing the production of proteins such as VEGFR and EGFR. Clear cell renal carcinoma images of people with this *VHL* gene mutation are shown in Figure 5(Linehan & Zbar, 2004; Pascual & Borque, 2008).

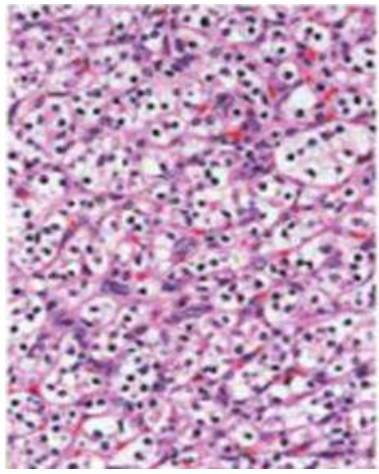

Figure 5. Cancerous tissue in kidney cells. The image shows a cross-section of samples taken from human renal epithelial neoplasm cells, and this type of clear cells became cancerous due to mutation in the *VHL* gene (Linehan & Zbar, 2004).

In addition to having an inherited mutated gene, acquired epigenetic changes and genetic mutations are also factors in the formation of renal cell carcinoma. Besides the *VHL* gene, which is frequently mutated in RCC, and various other genes play a role in the formation of cancerous cells, for example, mutations in genes such as *PBRM1* and *SETD2* play a role in the loss of heterozygosity of renal cells (Hsieh et al., 2017).

One of the non-hereditary diseases that may cause kidney cancer, cystic kidney disease occurs in patients with suppressed immune systems who receive dialysis treatment for more than a certain period of time. Papillary hyperplasia may occur in the kidney epithelial cells of people with cystic kidney disease, which may lead to the onset of cancer (Pascual & Borque, 2008). Hypertension can be mentioned as

another example that may play a role in the formation of cancer in the kidneys. According to research, one of the serious disease hypertension patients have a high risk of developing kidney cancer (Scelo & Larose, 2018).

4.4.2. Kidney Cancer Treatment with Chemotherapy

Systemic treatment, which can affect the whole body, or surgical treatment, which is a regional treatment, are generally used to treat kidney cancer. Here, by the decision taken by taking into consideration the patient's health condition and the stage of the cancer, partial nephrectomy, that is, the removal of the tumorous part, is performed in patients who can be operated on. Treatment methods such as drugs and immune system inhibitors are used for patients with metastasized kidney cancer, who are determined not to undergo surgery after evaluations (Hsieh et al., 2017).

When kidney cancer occurs in patients, it is treated with chemotherapy, but it is seen that the treatment becomes very difficult, especially in metastasized kidney cancers. To improve the treatment, cytotoxic agents are also given to patients in combination agents such as 5-FU, cisplatin, doxorubicin, floxuridine/FUDR can be used during this chemotherapy treatment (George et al., 2003). According to studies conducted on patients, improvements in tumor cells can be achieved when chemotherapy drugs such as floxuridine, 5-FUand vinblastine are used alone. Here, floxuridine and 5-fluorouracil block the DNA synthesis, and vinblastine stops the proliferation of tumor cells. Some phase studies on gemcitabine, another chemotherapy drug, also show

that it shows more effective results on cancer cells when given to patients in combination rather than alone (Thakur & Jain, 2011). According to studies conducted on patients with RCC, it has been revealed that gemcitabine combined with 5-FU has therapeutic effects on cancer. Consequence of phase II studies conducted in patients with metastasizing cancer cells, the combination of gemcitabine and oxaliplatin can be used on resistant cells. In addition, patients can be treated not only by combining chemotherapy drugs but also by combining chemotherapy drugs with immunotherapy drugs. According to a study, combining the chemotherapy drug gemcitabine with stimulants affecting the immune system, such as IFN and IL-2, shows that patients' tumor cells shrink (Lilleby & Fosså, 2005). As another combined drug therapy, vinblastine and 5-FU chemotherapy drugs are combined with the immune system stimulator biological agents interleukin (IL)-2 and interferon IFN-α and are used in kidney cancer patients (Ko et al., 2005).

4.4.3. Chemotherapy Toxicity Effects in Kidney Cancer

Generally used chemotherapy drugs may not have much effect on tumor cells in the kidney and cause toxicities, and therefore chemotherapy drugs are generally given to patients in combination with other drug groups for the treatment of kidney cancer (Ko et al., 2005). In line with the research, phase I and phase II studies, which include the combination of chemotherapy drugs and targeted drugs, have produced positive results on kidney cancer (Diamond et al., 2015).

Studies on the vinblastine, 5-FU, (IL)-2 and IFN-α drug regimen, which is created by combining chemotherapy drugs with other biological agents rather than combining them, show that it provides benefits to kidney cancer patients by causing tumor shrinkage and even disappearance. However, in addition to this benefit, some side effects may occur in patients receiving the treatment, these are typical toxicities such as nausea and depression (Ko et al., 2005). This treatment method, which consists of adding 13-cis-retinoic acid (13-C-RA) to the drug combination of vinblastine, 5-FU, (IL)-2 and also IFN-α used in the treatment of kidney cancer, was also tried and its side effects on the patients were recorded. While the positive tumor cell shrinkage occurred in the patients, toxicities such as fatigue, chills, fever, anorexia, and peripheral polyneuropathy also occurred and also, no specific toxicity was noted due to the addition of 13-C-RA to the combination (Atzpodien et al., 1995).

In studies conducted in kidney cancer patients using chemotherapy agents alone, no significant data could be obtained even when vinblastine was infused continuously (Diamond et al., 2015; Thakur & Jain, 2011). In studies conducted using another chemotherapy drug, gemcitabine, in patients, a small regression in cancer was observed (Diamond et al., 2015). In a phase II study, gemcitabine, when combined with other drugs, caused further shrinkage of tumor cells in the kidney (Thakur & Jain, 2011). According to a phase II study involving the combination of the chemotherapy drug gemcitabine with capecitabine, values from 84 patients who had previously received immunotherapy were examined. Toxicity occurred in more than half of

the patients, and tumor shrinkage was observed in a small portion. It is a combination that is not routinely used due to side effects such as neutropenia, hand-foot syndrome, thrombocytopenia, and fatigue, which generally occur in patients with metastasized kidney cancer (Tannir et al., 2008).

Some toxicities were detected as a result of phase studies of gemcitabine and doxorubicin, which can be used in the treatment of renal medullary carcinoma, a rare type of kidney cancer. According to Phase I studies, toxicities such as proteinuria, fatigue, hypertension, hand-foot syndrome, decreased appetite, weight loss, nausea, anemia, and thrombocytopenia occurred as a result of treatment. However, despite these toxicities, it is a tolerable treatment option because the survival time of patients who do not respond to platinum-based treatment is prolonged thanks to the use of gemcitabine and doxorubicin (Wilson et al., 2021).

A phase II study of the chemotherapy drug combination containing gemcitabine and 5-FU alone, using these chemotherapy drugs plus immunotherapy (IL)-2 and IFN-α, examined 39 patients with metastasized kidney cancer. While tumor sizes in patients have decreased, survival times have also been extended, and toxicities observed in patients are generally hematological (Buti et al., 2007).

It appears to be a partially well-tolerated treatment in studies using only 5-FU and gemcitabine in patients with kidney cancer. Toxicities caused by the use of this combination have been widely recorded as hematological and gastrointestinal. High levels of thymidylate synthase activity were detected in samples taken from

cancerous kidney cells, resulting from the effects of drugs (Ko et al., 2005).

Research shows that more effective drugs continue to be developed and researched because tumor cells are generally resistant to chemotherapy drugs. In this regard, it is generally thought that immunotherapy drugs can be used in combination with targeted drugs, because targeted treatments attack cells more specifically than chemotherapy. With this treatment, the amount of toxicity on healthy cells decreases and side effects decrease, so the combination of immunotherapy and targeted treatments allows for safer results (Thakur & Jain, 2011).

Sorafenib, an oral multiple tyrosine kinase (TK) inhibitor, which is one of the drugs used in targeted therapy in kidney cancer, prevents tumor tissue from angiogenesis. The phase III study on the use of Sunitinib, another tyrosine kinase inhibitor, showed that while the drug extends the lifespan of kidney cancer patients, it may have manageable side effects like general fatigue and high blood pressure level (Thakur & Jain, 2011). In addition, it has been determined that the negative changes in thyroid functions observed in patients are due to the use of sunitinib and sorafenib. Temsirolimus (Torisel), a drug approved by the FDA for kidney cancer, is a mammalian target of rapamycin inhibitor that prevents the proliferation of cancer cells. Studies conducted on the results of combining this drug with IFN-α did not show significant positive effects on patients, and fatigue, nausea, and hematological toxicities were observed. Axitinib is a drug that affects receptor tyrosine kinases, VEGFR1, VEGFR2 and PDGFR (platelet-derived growth

factor receptor). According to a phase II study in patients with metastatic kidney cancer, it had positive effects on tumor cells, while common side effects such as hoarseness, loss of appetite and chronic fatigue were observed. (Thakur & Jain, 2011).

4.5. Pancreatic Cancer

The pancreas is an organ plays a role in digestion process and body's homeostasis by secreting different hormones (Jennings et al., 2015). Cancer in the organ usually occurs due to epithelial proliferation in the pancreatic ducts. This type of cancer, which can reach advanced stages without giving specific symptoms, usually causes patients to die in a short time due to its high lethality rate. The disease is treated after diagnosis is made by endoscopic ultrasound or biopsy. Pancreatic cancer treatment can be done through surgery if it has not metastasized and chemotherapy treatment is usually continued after the surgery (Kamisawa et al., 2016). Significant risk factors for the development of pancreatic cancer include genetic inheritance, being overweight, having type 2 diabetes disease, and consumption of alcohol (Kleeff et al., 2016).

4.5.1. Pancreatic Cancer Mechanism

Malignant neoplasms commonly occurring in the pancreas are of the adenocarcinoma type consisting of epithelial cells. This abnormal appearance is examined in part A of Figure 6 and it is seen that the cells that proliferate abnormally in the epithelial cells of the pancreas organ are concentrated in the stroma part. Less common types of pancreatic

cancer include the neuroendocrine type, which arises from the hormone cells in the pancreas. An example of this type of cancer is examined in part B of Figure 6 and according to the section examined, the nuclei of cancer cells are distinct in this type of cancer. Another less common type of pancreatic cancer is acinar carcinoma, which consists of cells that produce digestive enzymes in the pancreas (Kleeff et al., 2016).

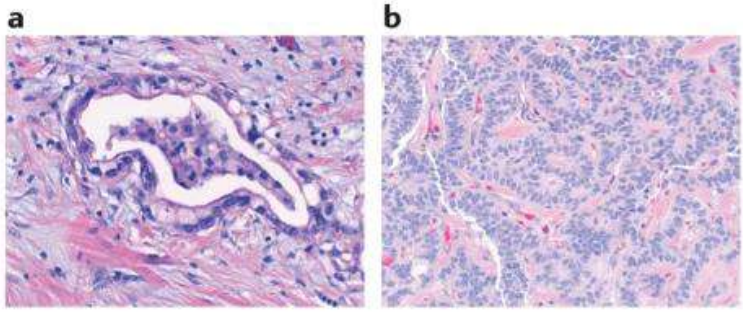

Figure 6. Cancerous tissues occur in pancreatic cells. Images of sections taken from cancer types occurring in pancreatic cells appear in parts a and b. Part a of the figure contains adenocarcinoma, that is, abnormal cancerous glands, which is the most common pancreatic cancer. In part b of the figure, there is a cross-section of neuroendocrine tumors, which is a type of pancreatic cancer that is not as common as adenocarcinoma. Here, cancerous cells generally form a clustered appearance, while their nuclei are visible (Kleeff et al., 2016).

There are some genes that play a significant role in the formation mechanism of pancreatic cancer, which is a lethal type of cancer.

Mutations in the *KRAS*, *CDKN2A*, *TP53* and *SMAD4* genes may cause cancerous cells to form in the pancreatic organ (Kamisawa et al., 2016). In addition to these genetic factors, environmental, epigenetic and metabolomic changes may cause tumor cell formation in the pancreas (Kleeff et al., 2016). In the development of pancreatic cancer, which is the lethal type of cancer among all cancer types, growth factors cause cells to become overexpressed and become cancerous, and degradation of the signaling pathways here plays a role in tumor cell formation. For example, signal degradation occurring in the JAK/STAT signal communication pathway may cause pancreatic cancer development (Güngör et al., 2013).

4.5.2 Pancreatic Cancer Treatment with Chemotherapy

While gemcitabine has been used as a single agent in chemotherapy drug treatment, which is one of the main treatment methods for pancreatic cancer, for many years, it has been determined in clinical trials that it can also provide benefits to tumor cells by giving chemotherapy drugs in combination. In these clinical studies, for example, in the PRODIGE6 clinical study, it was seen that the drug combination of FOLFIRINOX (5-FU, folinic acid, irinotecan and oxaliplatin) and gemcitabine/nab-paclitaxe was more effective when given in combination rather than given alone, and it became a standard treatment method (Saung & Zheng, 2017). While phase III studies on the drug combination of 5-FU and oxaliplatin, which can be used in the treatment of pancreatic cancer, are ongoing, this combination has not yet been considered as a standard treatment and its effectiveness is not

certain. According to another study, the use of the chemotherapy drug S-1 as a single agent was compared with the use of the drug gemcitabine as a single agent, and S-1 was found to be more effective and began to be used as a standard treatment (Saung & Zheng, 2017).

Chemotherapy drugs are not only combined with each other, but in line with the studies, the chemotherapy drug gemcitabine, and the EGFR inhibitor erlotinib, approved by the FDA, are used. Another drug combination approved by the FDA for pancreatic cancer is the combination of gemcitabine and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) (Kleeff et al., 2016). In accordance with the decision made considering the clinical condition of the patient, chemotherapy treatment is then continued in patients whose pancreas is removed by surgery, where gemcitabine or S-1 is generally used, while for patients who are not operated on, FOLFIRINOX, nab-paclitaxel, and gemcitabine combination is used.(Kamisawa et al., 2016). One of the most used drug combinations for the treatment of pancreatic cancer, which can usually occur in advanced stages at older ages, is the combination of FOLFIRINOX, Abraxane and gemcitabine drugs (Li et al., 2020). Chemotherapy drugs can also be used in combination with immunotherapy drugs for the treatment of pancreatic cancer. Phase studies show that patients who received chemotherapy simultaneously with the nivolumab immunotherapy drug experienced a positive prolongation in life expectancy, so it can continue to be investigated and be seen as an alternative treatment method for patients with advanced pancreatic cancer (Padrón et al., 2022).

4.5.3 Chemotherapy Toxicity Effects in Pancreatic Cancer

Although chemotherapy is intended to treat pancreatic cancer with drug therapy, sometimes toxicities may occur and disruptions in treatment may occur. Side effects such as significant hematological toxicities, thrombocytopenia and neutropenia have occurred in some of the patients receiving gemcitabine, one of the most commonly used chemotherapy drugs during pancreatic treatment (Okazaki et al., 2010). According to studies, gemcitabine is inactivated by the CDA enzyme and because of the examination of some pancreatic cancer patients, it has been observed that differences in this CDA producing gene may reduce the effectiveness of gemcitabine and even cause toxicity (Okazaki et al., 2010).

Treatment can go badly when cancer cells develop resistance to this drug, which is frequently used for pancreatic cancer. In addition, side effects such as shortness of breath, nausea, and kidney dysfunction limit the use of this drug for patients (Amrutkar & Gladhaug, 2017).

A phase III study on the use of S-1 chemotherapy drug used in patients with metastasized pancreatic cancer was compared with patients using gemcitabine and it was found that S-1 was as beneficial as gemcitabine. In terms of side effects, patients using S-1 generally experienced digestive system-related toxicities such as diarrhea and weight loss (Ying et al., 2012). While healing effects were observed by giving combined drugs to patients during pancreatic treatment, gemcitabine, and the chemotherapy drug irinotecan, which works as a topoisomerase enzyme inhibitor, were combined and given to patients.

While average life expectancy was prolonged with treatment, serious hematological toxicity also occurred in patients (Ying et al., 2012).

According to a phase II study with the FOLFIRINOX drug combination used during pancreatic cancer treatment, while cure rates increased in patients, toxicities such as neutropenia continued to occur. According to other phase studies, hematological toxicities such as neutropenia, anemia, fatigue, vomiting, and diarrhea continued to occur frequently in patients. One of the patients participating in the phase study died due to febrile neutropenia, so FOLFIRINOX generally gives better results for patients with near-normal, non-advanced pancreatic cancer with metastases (Conroy et al., 2011).

According to a study, chemotherapy treatment was given to 89 patients after pancreas surgery, and drugs such as 5-FU, cisplatin and Interferon-alpha-2b were used regularly for certain periods. In this treatment, which mostly involves the use of 5-FU, some toxicities have occurred and changed the course of the treatment. In general, acute toxicity was observed in almost all these patients, and among the common side effects, hematological toxicities, hepatic toxicities, that is, abnormal increases in liver enzyme values, neurological toxicities such as depression and fainting, cardiovascular toxicities such as blood pressure, dermatological and gastrointestinal toxicities such as hair loss and itching occurred in the patients (V.J. et al., 2011).

One of another study conducted in 2018, patients with pancreatic cancer were treated using the drug combination nab-paclitaxel, gemcitabine and FOLFIRINOX. As a result of the examination of the patients, survival times increase, and although older patients are more

prone to toxicities, they can be cured by using this treatment method. In all pancreatic cancer patients included in the study, toxicities resulting from these drug combinations were generally seen as anemia, infection, fatigue, diarrhea, vomiting, and an increase in the lower liver level (Li et al., 2020).

The effectiveness of immunotherapy drugs alone in pancreatic cancer treatment is low, and one of the main reasons for this is that the T cells in the treatment cannot pass through the tissue with dense stroma in the pancreas and reach the cancerous cells, thus not being able to treat them (Chrysostomou et al., 2023). Although studies using the immunotherapy drug nivolumab and the chemotherapy drugs nab paclitaxel and gemcitabine showed that the combination was safe, there were serious toxicities in patients. In this treatment, toxicities that occur frequently include respiratory failure, leukopenia, neutropenia, nausea, diarrhea, increase in liver enzyme values, muscle weakness, hypothyroidism, and colitis (Chrysostomou et al., 2023).

4.6. Spleen Cancer

Spleen is a lymphoid organ that takes role in the immune system and has functions such as stimulating and clearing foreign substances in the blood by antigen-presenting cells (APC), and eliminating red blood cells that cannot correctly fulfill their function (Lewis et al., 2019; Mebius & Kraal, 2005). The appearance of tumor tissue in this organ is generally rare, and the diagnosis of this type of cancer, which usually does not cause symptoms for a long time, is difficult. Benign or malignant tumors occurring in patients can be treated by splenectomy,

that is, surgical removal of the spleen. Malignant tumors in the spleen are treated with splenectomy, chemotherapy, and radiotherapy. It is known that this rare type of cancer is usually diagnosed after the age of 50 and is more common in women than men (Fotiadis et al., 2009). Early diagnosis of spleen cancer, which has a high lethality rate, saves the lives of patients (Hamid et al., 2010).

4.6.1. Spleen Cancer Mechanism

There are some mechanisms that may trigger cancer in the spleen, such as: Primary splenic angiosarcomas, which occur in the vessels of the spleen, are among the rare and fatal cancer types. This type of cancer, which often causes abdominal pain, can multiply rapidly, spread to the lymph nodes and metastasize (Hamid et al., 2010). It is known that the disease usually metastasizes to vital organs such as the liver, lungs, and bones. Hodgkin's rare disease one is a mechanism that may cause cancer in the spleen due to lymphomas (Fotiadis et al., 2009). Tumor formation of this disease, which occurs in lymphomas, needs to be kept under control as it can cause cancer in advanced stages (Arya et al., 2004). Also, it is known non-Hodgkin lymphoma can cause cancer in the spleen in people. The tumor mass formed by involvement in this organ increases the volume of the organ and begins to manifest itself with side effects. The type of lymphoma that causes the disease, its appearance, and the symptoms of the disease differ from Hodgkin lymphoma (Fotiadis et al., 2009). The case in point non-Hodgkin lymphoma includes rapidly growing Burkitt lymphoma, T-cell lymphomas, diffuse large B cell-derived lymphomas, and lymphomas

(McCarten et al., 2019). Another mechanism of occurring sarcomas is tumor cells that are not connected to lymphoids that may cause cancer in the spleen. These tumors, which can originate from the tissues in the spleen, can rarely form from the fatty tissues or fibroblasts there and can give way to cancerous tissues as they progress (Fotiadis et al., 2009).

4.6.2. Spleen Cancer Treatment with Chemotherapy

Among the treatments for spleen cancer, splenectomy, which is the surgical removal of the spleen by entering from the abdominal area, can be performed. Treatment is tailored to ensure that there are no potentially fatal conditions such as splenic rupture in patients (Fotiadis et al., 2009; Hamid et al., 2010). Other treatment methods include radiation and chemotherapy, although this type of cancer is generally resistant to chemotherapy. Chemotherapy drugs used in patients with diagnosed splenic angiosarcoma include the combination of gemcitabine and docetaxel (Hamid et al., 2010). In addition, the 5-FU chemotherapy drug can be used during treatment instead of gemcitabine in patients whose spleen has not been removed surgically (Donahue et al., 2010). When chemotherapy treatment is continued after splenectomy, drugs such as cyclophosphamide, hydrodoxorubicin, vincristine and prednisolone can be given to patients, and drug combinations containing fludarabine are generally used in the spleen cancer treatment process (Milosevic et al., 2009).

For the treatment of spleen cancer caused by non-Hodgkin's lymphoma, a single-agent chemotherapy drug regimen consisting of

cyclophosphamide, vincristine and fotretamine is used in some patients, while in some patients CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), COP (cyclophosphamide, vincristine, prednisolone), CVChlP (cyclophosphamide vinblastine, chlorambucil, prednisolone) such as combined chemotherapy treatments are used by adjusting them to best suit the characteristics of the patients (Musteata et al., 2004). As a result of primary angiosarcoma occurring in the spleen, anthracycline, ifosfamide and taxane chemotherapy drug groups are frequently used, while drug regimens consisting of cyclophosphamide, bevacizumab, doxorubicin, paclitaxel, epirubicin, ifosfamide, vincristine, etoposide, docetaxel, dacarbazine, and cis-platinum are also used (Ferreira et al., 2012). After the chemotherapy treatments are given to the patients, if deemed appropriate, the treatments can be continued by giving immunotherapy drugs such as pembrolizumab alone or in combination with chemotherapy drugs (Wheelwright et al., 2021).

4.6.3. Chemotherapy Toxicity Effects in Spleen Cancer

When treating spleen cancer, which is a difficult type of cancer, with chemotherapy, serious toxicities can often occur. The use of drug gemcitabine, which is frequently used in the chemotherapy treatment of spleen cancer, blocks platelet production in patients, so any bleeding that may occur in patients carries the risk of toxicity that causes a stopping effect on chemotherapy treatment, as it has the possibility of reaching serious levels (Donahue et al., 2010). On the other hand, hypersplenism, that is, spleen enlargement, often occurs in these

patients, which has a limiting effect on chemotherapy treatment. In addition, while patients are being treated with platinum-based chemotherapy drugs combined with gemcitabine, treatment is limited in case of severe toxicities such as anemia and leukopenia (Donahue et al., 2010). In phase II studies conducted by combining the drug gemcitabine, used in the treatment of the pancreas, with the drug docetaxel from the semi-synthetic taxon group, toxicities such as thrombocytopenia, leukopenia, nausea, and stomatitis occurred in patients, which would stop the treatment (Sahora et al., 2011). Splenic cancer treatment is aimed by administering chemotherapy drug combinations containing CHOP and fludarabine, FMD (fludarabine, mitoxantrone, dexazone), FMC (fludarabine, mitoxantrone, cyclophosphamide) to patients with splenic marginal zone lymphoma, with or without splenectomy. It has been observed that hematological toxicities such as anemia, high leukocyte count, leukocytopenia, lymphocytosis, and thrombocytopenia occur with the use of these drugs in a certain group of patients, but there are also improvements in survival time (Milosevic et al., 2009).

According to studies conducted in non-Hodgkin lymphoma patients using the COP chemotherapy drug combination, hair loss and decreases in blood cells are among the important side effects. In addition, according to the comparison in the study, it was noted that replacing bendamustine with cyclophosphamide resulted in less toxicity and provided more benefits to patients (Herold et al., 2006). Phase II studies using the chemotherapy drug paclitaxel for the treatment of angiosarcoma spleen cancer showed that the survival of

patients was prolonged, but toxicities also occurred. In a study conducted with a total of 30 people, one person died due to severe thrombocytopenia toxicity, while serious toxicities occurred in 7 patients (Wheelwright et al., 2021).

Some important studies have shown that chemotherapy drugs used to treat Hodgkin's disease increase the likelihood of cancer types such as leukemia or solid tumors in patients. In the study, it was determined that the risk of developing leukemia increased in patients when chlorambucil, procarbazine, and vinblastine drugs were given alone or in combination or after splenectomy (Boivin et al., 1995). Nivolumab, an immunotherapy drug for Hodgkin lymphoma, works by enabling the patient's immune system to fight against cancer cells. By giving this drug to patients who had previously received chemotherapy treatment, positive results began to be achieved in the treatment of patients after a certain period (Maly & Alinari, 2016). In addition to positive results, toxicities were also observed, and these toxicities were generally recorded as tolerable side effects such as skin rash, thrombocytopenia, neuropathy, and pancreatitis. Another immunotherapy drug, pembrolizumab, binds better to the PD-1 protein and blocks it, thus enabling immune cell T cells to attack cancer cells better. It is approved by the FDA and used in other types of cancer as a better-tolerated immunotherapy drug. In clinical studies conducted in classical Hodgkin lymphoma patients, toxicities such as thyroid hormone disorder, diarrhea, pneumonitis, liver enzyme disorder and colitis occurred (Maly & Alinari, 2016).

5. CONCLUSION

Given these points, specific interactions may occur in healthy cells as well as cancer cells in chemotherapy drug treatment which aims to prevent and destroy the uncontrolled and abnormal proliferation of cancer cells. These interactions cause toxicities and serious side effects in patients receiving the chemotherapy treatment. The reason why the treatment methods applied to patients are diverged to plan the most appropriate treatment method for the patient, considering the person's health condition, cancer type and cancer stage. The results of the several phase studies discussed above this view. In different types of cancer, factors such as metabolism, gender, age, overweight, diet, previous diseases such as viruses, and hereditary predispositions can change the reactions of patients to drugs, and toxicities may occur as a result.

To reduce toxicities of various treatments several steps can be taken. For example-adjustment of the drug dose given to patients, combination drugs with chemotherapy or other treatment drugs, and change of the administration route can be performed. In addition to the cancer therapeutic effects of chemotherapy drugs given to patients, it has been observed that negative effects such as gastrointestinal toxicity, neurotoxicity, hematological toxicity, hepatoxicity, nephrotoxicity, heart toxicity and lung toxicity frequently occur. In addition to these toxicities, patients may experience severe fatigue, hair and skin rashes, drowsiness, muscle cramps, abdominal pain, infection, liver enzyme changes, migraines, high fever, and deterioration in the immune system. While toxicities resulting from chemotherapy treatment may decrease

over time after the treatment process is completed, phase studies have revealed that some patients do not show lifelong recovery and left the treatment with permanent effects.

In this article, the toxicities that occur in the same or different cancer types because of the application of different chemotherapy drug combinations to patients are examined. Thanks to continuous addition of new information to the literature and with future drug phase studies we believe toxicity risks of the chemotherapy treatment can be minimized.

6. REFERENCES

Ahmed, F. E. (2003). Colon Cancer: Prevalence, Screening, Gene Expression and Mutation, and Risk Factors and Assessment. In Journal of Environmental Science and Health - Part C Environmental Carcinogenesis and Ecotoxicology Reviews (Vol. 21, Issue 2). https://doi.org/10.1081/GNC-120026233

Ahmed, M. (2020). Colon Cancer: A Clinician's Perspective in 2019. Gastroenterology Research, 13(1), 1–10. https://doi.org/10.14740/gr1239

Ajani, J. A. (2008). Optimizing docetaxel chemotherapy in patients with cancer of the gastric and gastroesophageal junction: Evolution of the docetaxel, cisplatin, and 5-fluorouracil regimen. Cancer, 113(5). https://doi.org/10.1002/cncr.23661

Akhila, J. S., Shyamjith, Deepa, & Alwar, M. C. (2007). Acute toxicity studies and determination of median lethal dose. In Current Science (Vol. 93, Issue 7).

Alfarouk, K. O., Stock, C. M., Taylor, S., Walsh, M., Muddathir, A. K., Verduzco, D., Bashir, A. H. H., Mohammed, O. Y., Elhassan, G. O., Harguindey, S., Reshkin, S. J., Ibrahim, M. E., & Rauch, C. (2015). Resistance to cancer chemotherapy: Failure in drug response from ADME to P-gp. In Cancer Cell International (Vol. 15, Issue 1). https://doi.org/10.1186/s12935-015-0221-1

Alim, A., Sharmin, R., Park, D., & Anisuzzaman, A. S. M. (2020). Gastric Cancer and Its Remedy. https://doi.org/10.1007/978-981-15-5471-1_9

Amrutkar, M., & Gladhaug, I. P. (2017). Pancreatic cancer chemoresistance to gemcitabine. In Cancers (Vol. 9, Issue 11). https://doi.org/10.3390/cancers9110157

Anand, P., Kunnumakara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., Sung, B., & Aggarwal, B. B. (2008). Cancer is a preventable disease that requires major lifestyle changes. In Pharmaceutical Research (Vol. 25, Issue 9). https://doi.org/10.1007/s11095-008-9661-9

Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A., Dhanjal, J. K., Dewanjee, S., Vallamkondu, J., & Pérez de la Lastra, J. M. (2023). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. In Genes and Diseases (Vol. 10, Issue 4, pp. 1367–1401). KeAi Communications Co. https://doi.org/10.1016/j.gendis.2022.02.007

André, T., Lonardi, S., Wong, K. Y. M., Lenz, H. J., Gelsomino, F., Aglietta, M., Morse, M. A., Van Cutsem, E., McDermott, R., Hill, A., Sawyer, M. B., Hendlisz, A., Neyns, B., Abdullaev, S., Memaj, A., Lei, M., Dixon, M., Kopetz, S., & Overman, M. J. (2022). Nivolumab plus low-dose ipilimumab in previously treated patients with

microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Annals of Oncology, 33(10). https://doi.org/10.1016/j.annonc.2022.06.008

Anwanwan, D., Singh, S. K., Singh, S., Saikam, V., & Singh, R. (2020). Challenges in liver cancer and possible treatment approaches. In Biochimica et Biophysica Acta - Reviews on Cancer (Vol. 1873, Issue 1). https://doi.org/10.1016/j.bbcan.2019.188314

Arivazhahan, A. (2022). Principles of EC50, ED50, pD2 and pA2 Values of Drugs. In Introduction to Basics of Pharmacology and Toxicology: Volume 3: Experimental Pharmacology: Research Methodology and Biostatistics (Vol. 3). https://doi.org/10.1007/978-981-19-5343-9_10

Arya, L. S., Dinand, V., Bakhshi, S., Thavaraj, V., Singh, R., & Dawar, R. (2004). Significance of splenomegaly in childhood Hodgkin disease. Journal of Pediatric Hematology/Oncology, 26(12).

Asghar, U., & Meyer, T. (2012). Are there opportunities for chemotherapy in the treatment of hepatocellular cancer? In Journal of Hepatology (Vol. 56, Issue 3). https://doi.org/10.1016/j.jhep.2011.07.031

Atzpodien, J., Kirchner, H., Duensing, S., Hänninen, E. L., Franzke, A., Buer, J., Probst, M., Anton, P., & Poliwoda, H. (1995). Biochemotherapy of advanced metastatic renal-cell carcinoma: results of the combination of interleukin-2,

alpha-interferon, 5-fluorouracil, vinblastine, and 13-cis-retinoic acid. World Journal of Urology, 13(3). https://doi.org/10.1007/BF00184875

Aznab, M., Beiki, O., pia, K. E., Setayeshi, K., Hesami, M. A., & Vrae, H. (2017). Evaluation the Survival of Patients with Gastric Cancer Treated with Adjuvant or Palliative Chemotherapy. Journal of Gastrointestinal Cancer, 48(1). https://doi.org/10.1007/s12029-016-9868-7

Bakrania, A., Joshi, N., Zhao, X., Zheng, G., & Bhat, M. (2023). Artificial intelligence in liver cancers: Decoding the impact of machine learning models in clinical diagnosis of primary liver cancers and liver cancer metastases. Pharmacological Research, 189. https://doi.org/10.1016/j.phrs.2023.106706

Battista, S., Ambrosio, M. R., Limarzi, F., Gallo, G., & Saragoni, L. (2021). Molecular alterations in gastric preneoplastic lesions and early gastric cancer. In International Journal of Molecular Sciences (Vol. 22, Issue 13). https://doi.org/10.3390/ijms22136652

Benson, A. B., Venook, A. P., Cederquist, L., Chan, E., Chen, Y. J., Cooper, H. S., Deming, D., Engstrom, P. F., Enzinger, P. C., Fichera, A., Grem, J. L., Grothey, A., Hochster, H. S., Hoffe, S., Hunt, S., Kamel, A., Kirilcuk, N., Krishnamurthi, S., Messersmith, W. A., … Freedman-Cass, D. (2017). Colon cancer, version 1.2017: Clinical practice guidelines in oncology. In JNCCN Journal of the National

Comprehensive Cancer Network (Vol. 15, Issue 3). https://doi.org/10.6004/jnccn.2017.0036

Boige, V., Raoul, J. L., Pignon, J. P., Bouché, O., Blanc, J. F., Dahan, L., Jouve, J. L., Dupouy, N., & Ducreux, M. (2007). Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. British Journal of Cancer, 97(7). https://doi.org/10.1038/sj.bjc.6603956

Boivin, J. F., Hutchison, G. B., Zauber, A. G., Bernstein, L., Davis, F. G., Michel, R. P., Zanke, B., Tan, C. T. C., Fuller, L. M., Mauch, P., & Ultmann, J. E. (1995). Incidence of second cancers in patients treated for hodgkin's disease. Journal of the National Cancer Institute, 87(10). https://doi.org/10.1093/jnci/87.10.732

Breakstone, R. (2021). Colon cancer and immunotherapy—can we go beyond microsatellite instability? In Translational Gastroenterology and Hepatology (Vol. 6). https://doi.org/10.21037/TGH.2020.03.08

Buti, S., Brighenti, M., Bongiovanni, C., Buzio, C., Chiesa, M. D., Alberici, F., & Passalacqua, R. (2007). Role of chemotherapy with gemcitabine plus 5-fluorouracil and chemoimmunotherapy in metastatic renal cell cancer (mRCC). Journal of Immunotherapy, 30(7). https://doi.org/10.1097/CJI.0b013e31814fb2ec

Chansky, K., Benedetti, J., & Macdonald, J. S. (2005). Differences in toxicity between men and women treated with 5-

fluorouracil therapy for colorectal carcinoma. Cancer, 103(6). https://doi.org/10.1002/cncr.20878

Cheng, F., Zhang, R., Sun, C., Ran, Q., Zhang, C., Shen, C., Yao, Z., Wang, M., Song, L., & Peng, C. (2023). Oxaliplatin-induced peripheral neurotoxicity in colorectal cancer patients: mechanisms, pharmacokinetics and strategies. In Frontiers in Pharmacology (Vol. 14). https://doi.org/10.3389/fphar.2023.1231401

Chhikara, B. S., & Parang, K. (n.d.). Chemical Biology LETTERS Global Cancer Statistics 2022: the trends projection analysis. In Chemical Biology Letters Chem. Biol. Lett (Vol. 2023, Issue 1). https://pubs.thesciencein.org/cbl

Chrysostomou, D., Roberts, L. A., Marchesi, J. R., & Kinross, J. M. (2023). Gut Microbiota Modulation of Efficacy and Toxicity of Cancer Chemotherapy and Immunotherapy. In Gastroenterology (Vol. 164, Issue 2). https://doi.org/10.1053/j.gastro.2022.10.018

Cienfuegos, J. A., Baixauli, J., Beorlegui, C., Ortega, P. M., Granero, L., Zozaya, G., & Hernández Lizoáin, J. L. (2018). The impact of major postoperative complications on long-term outcomes following curative resection of colon cancer. International Journal of Surgery, 52. https://doi.org/10.1016/j.ijsu.2018.03.001

Conroy, T., Desseigne, F., Ychou, M., Bouché, O., Guimbaud, R., Bécouarn, Y., Adenis, A., Raoul, J.-L., Gourgou-Bourgade, S., de la Fouchardière, C., Bennouna, J., Bachet, J.-B.,

Khemissa-Akouz, F., Péré-Vergé, D., Delbaldo, C., Assenat, E., Chauffert, B., Michel, P., Montoto-Grillot, C., & Ducreux, M. (2011). FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. New England Journal of Medicine, 364(19). https://doi.org/10.1056/nejmoa1011923

Correa, P. (1992). Human Gastric Carcinogenesis: A Multistep and Multifactorial Process- First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Research, 52(24).

Croce, C. M. (2008). molecular origins of cancer Oncogenes and Cancer. In N Engl J Med (Vol. 358). www.nejm.org

Curigliano, G., Cardinale, D., Dent, S., Criscitiello, C., Aseyev, O., Lenihan, D., & Cipolla, C. M. (2016). Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA: A Cancer Journal for Clinicians, 66(4). https://doi.org/10.3322/caac.21341

Danilović, M., Isailović, J., Aleksić, I., Džambas, J., & Marinković, N. (2020). Accidental colchicine poisoning with fatal outcome after ingestion of meadow saffron (Colchicum autumnale L.). Vojnosanitetski Pregled, 77(10). https://doi.org/10.2298/VSP180413034D

De Santa Barbara, P., Van Den Brink, G. R., & Roberts, D. J. (2003). Development and differentiation of the intestinal epithelium. In Cellular and Molecular Life Sciences (Vol. 60, Issue 7). https://doi.org/10.1007/s00018-003-2289-3

De Vivo, R., Pignata, S., Palaia, R., Parisi, V., & Daniele, B. (2000). The role of chemotherapy in the management of gastric cancer. In Journal of Clinical Gastroenterology (Vol. 30, Issue 4). https://doi.org/10.1097/00004836-200006000-00004

Delaunoit, T. (2011). Latest developments and emerging treatment options in the management of stomach cancer. Cancer Management and Research. https://doi.org/10.2147/cmr.s12713

DeVita, V. T., & Chu, E. (2008). A history of cancer chemotherapy. In Cancer Research (Vol. 68, Issue 21). https://doi.org/10.1158/0008-5472.CAN-07-6611

Diamond, E., Molina, A. M., Carbonaro, M., Akhtar, N. H., Giannakakou, P., Tagawa, S. T., & Nanus, D. M. (2015). Cytotoxic chemotherapy in the treatment of advanced renal cell carcinoma in the era of targeted therapy. In Critical Reviews in Oncology/Hematology (Vol. 96, Issue 3). https://doi.org/10.1016/j.critrevonc.2015.08.007

Dimaras, H., Corson, T. W., Cobrinik, D., White, A., Zhao, J., Munier, F. L., Abramson, D. H., Shields, C. L., Chantada, G. L., Njuguna, F., & Gallie, B. L. (2015). Retinoblastoma. Nature Reviews Disease Primers, 1. https://doi.org/10.1038/nrdp.2015.21

Donahue, T. R., Kazanjian, K. K., Isacoff, W. H., Reber, H. A., & Hines, O. J. (2010). Impact of splenectomy on thrombocytopenia, chemotherapy, and survival in patients

with unresectable pancreatic cancer. Journal of Gastrointestinal Surgery, 14(6). https://doi.org/10.1007/s11605-010-1187-x

Donne, R., & Lujambio, A. (2023). The liver cancer immune microenvironment: Therapeutic implications for hepatocellular carcinoma. In Hepatology (Vol. 77, Issue 5). https://doi.org/10.1002/hep.32740

Dosset, M., Vargas, T. R., Lagrange, A., Boidot, R., Végran, F., Roussey, A., Chalmin, F., Dondaine, L., Paul, C., Marie-Joseph, E. L., Martin, F., Ryffel, B., Borg, C., Adotévi, O., Ghiringhelli, F., & Apetoh, L. (2018). PD-1/PD-L1 pathway: an adaptive immune resistance mechanism to immunogenic chemotherapy in colorectal cancer. OncoImmunology, 7(6). https://doi.org/10.1080/2162402X.2018.1433981

Dougan, M. (2020). Understanding and overcoming the inflammatory toxicities of immunotherapy. Cancer Immunology Research, 8(10). https://doi.org/10.1158/2326-6066.CIR-20-0372

Drott, J., Starkhammar, H., Kjellgren, K., & Berterö, C. (2018). Neurotoxic side effects early in the oxaliplatin treatment period in patients with colorectal cancer. Oncology Nursing Forum, 45(6). https://doi.org/10.1188/18.ONF.690-697

Eatrides, J., Wang, E., Kothari, N., & Kim, R. (2017). Role of Systemic Therapy and Future Directions for Hepatocellular

Carcinoma. In Cancer Control (Vol. 24, Issue 3). https://doi.org/10.1177/1073274817729243

Edge, S. B., & Compton, C. C. (2010). The american joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. In Annals of Surgical Oncology (Vol. 17, Issue 6). https://doi.org/10.1245/s10434-010-0985-4

Ekanayake Weeramange, C., Tang, K. D., Barrero, R. A., Hartel, G., Liu, Z., Ladwa, R., Langton-Lockton, J., Frazer, I., Kenny, L., Vasani, S., & Punyadeera, C. (2023). Salivary micro RNAs as biomarkers for oropharyngeal cancer. Cancer Medicine, 12(14). https://doi.org/10.1002/cam4.6185

Feng, M., Pan, Y., Kong, R., & Shu, S. (2020). Therapy of Primary Liver Cancer. In Innovation (Vol. 1, Issue 2). Cell Press. https://doi.org/10.1016/j.xinn.2020.100032

Ferreira, B. P., Rodler, E. T., Loggers, E. T., Pollack, S. M., & Jones, R. L. (2012). Systemic therapy in primary angiosarcoma of the spleen. In Rare Tumors (Vol. 4, Issue 4). https://doi.org/10.4081/rt.2012.e55

Ferrer-Mayorga, G., Larriba, M. J., Crespo, P., & Muñoz, A. (2019). Mechanisms of action of vitamin D in colon cancer. In Journal of Steroid Biochemistry and Molecular Biology (Vol. 185). https://doi.org/10.1016/j.jsbmb.2018.07.002

Finco, D. R. (1997). Chapter 17 - Kidney Function. Clinical Biochemistry of Domestic Anymals.

Finlay A Macrae, M. (2018). Colorectal cancer: Epidemiology, risk factors, and protective factors. In UptoDate.

Fotiadis, C. I., Georgopoulos, I., Stoidis, C., & Patapis, P. (2009). Primary tumors of the spleen. In International Journal of Biomedical Science (Vol. 5, Issue 2). https://doi.org/10.59566/ijbs.2009.5085

Gao, Y., Shang, Q., Li, W., Guo, W., Stojadinovic, A., Mannion, C., Man, Y. G., & Chen, T. (2020). Antibiotics for cancer treatment: A double-edged sword. Journal of Cancer, 11(17). https://doi.org/10.7150/jca.47470

George, C. M., Stadler, W. M., & Figlin, R. A. (2003). 0. THE ROLE OF SYSTEMIC CHEMOTHERAPY IN THE TREATMENT OF KIDNEY CANCER.

Giovannucci, E., & Willett, W. C. (1994). Dietary factors and risk of colon cancer. Annals of Medicine, 26(6). https://doi.org/10.3109/07853899409148367

Goss, K. H., & Groden, J. (2000). Biology of the adenomatous polyposis coli tumor suppressor. Journal of Clinical Oncology, 18(9). https://doi.org/10.1200/JCO.2000.18.9.1967

Grazie, M. Le, Biagini, M. R., Tarocchi, M., Polvani, S., & Galli, A. (2017). Chemotherapy for hepatocellular carcinoma: The present and the future. In World Journal of Hepatology (Vol. 9, Issue 21). https://doi.org/10.4254/wjh.v9.i21.907

Gullo, I., Grillo, F., Mastracci, L., Vanoli, A., Carneiro, F., Saragoni, L., Limarzi, F., Ferro, J., Parente, P., & Fassan,

M. (2020). Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes. In Pathologica (Vol. 112, Issue 3). https://doi.org/10.32074/1591-951X-166

Güngör, C., Hofmann, B. T., Wolters-Eisfeld, G., Bockhorn, M., & Güngör, C. (2013). Pancreatic cancer Correspondence LINKED ARTICLES. https://doi.org/10.1111/bph.2014.171.issue-4

Hamid, K. S., Rodriguez, J. A., & Lairmore, T. C. (2010). Primary splenic angiosarcoma. Journal of the Society of Laparoendoscopic Surgeons, 14(3). https://doi.org/10.4293/108680810X12924466006521

Hancock, S. B., & Georgiades, C. S. (2016). Kidney Cancer Definition and Epidemiology. www.journalppo.com

Hatano, Y., Tamada, M., Matsuo, M., & Hara, A. (2020). Molecular Trajectory of BRCA1 and BRCA2 Mutations. In Frontiers in Oncology (Vol. 10). Frontiers Media S.A. https://doi.org/10.3389/fonc.2020.00361

Herold, M., Schulze, A., Niederwieser, D., Franke, A., Fricke, H. J., Richter, P., Freund, M., Ismer, B., Dachselt, K., Boewer, C., Schirmer, V., Weniger, J., Pasold, R., Winkelmann C Klinkenstein, C., Schulze, M., Arzberger, H., Bremer, K., Hahnfeld, S., Schwarzer, A., … Müller, C. (2006). Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle

cell lymphoma: Results of a randomised phase III trial (OSHO# 19). Journal of Cancer Research and Clinical Oncology, 132(2). https://doi.org/10.1007/s00432-005-0023-2

Hoekstra, L. T., De Graaf, W., Nibourg, G. A. A., Heger, M., Bennink, R. J., Stieger, B., & Van Gulik, T. M. (2013). Physiological and biochemical basis of clinical liver function tests: A review. In Annals of Surgery (Vol. 257, Issue 1). https://doi.org/10.1097/SLA.0b013e31825d5d47

Hoering, A., LeBlanc, M., & Crowley, J. (2011). Seamless phase I-II trial design for assessing toxicity and efficacy for targeted agents. Clinical Cancer Research, 17(4). https://doi.org/10.1158/1078-0432.CCR-10-1262

Horstmann, E., McCabe, M. S., Grochow, L., Yamamoto, S., Rubinstein, L., Budd, T., Shoemaker, D., Emanuel, E. J., & Grady, C. (2005). Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002. New England Journal of Medicine, 352(9). https://doi.org/10.1056/nejmsa042220

Hsieh, J. J., Purdue, M. P., Signoretti, S., Swanton, C., Albiges, L., Schmidinger, M., Heng, D. Y., Larkin, J., & Ficarra, V. (2017). Renal cell carcinoma. Nature Reviews Disease Primers, 3. https://doi.org/10.1038/nrdp.2017.9

Hunt, R. H., Camilleri, M., Crowe, S. E., El-Omar, E. M., Fox, J. G., Kuipers, E. J., Malfertheiner, P., McColl, K. E. L., Pritchard, D. M., Rugge, M., Sonnenberg, A., Sugano, K.,

& Tack, J. (2015). The stomach in health and disease. Gut, 64(10). https://doi.org/10.1136/gutjnl-2014-307595

Igaue, S., Okuno, T., Ishibashi, H., Nemoto, M., Hiyoshi, M., Kawasaki, H., Saitoh, H., Saitoh, M., Akagi, K., & Yamamoto, J. (2022). A pathological complete response after nivolumab plus ipilimumab therapy for DNA mismatch repair-deficient/microsatellite instability-high metastatic colon cancer: A case report. Oncology Letters, 24(1). https://doi.org/10.3892/ol.2022.13332

Ilic, M., & Ilic, I. (2022). Epidemiology of stomach cancer. In World Journal of Gastroenterology (Vol. 28, Issue 12). https://doi.org/10.3748/wjg.v28.i12.1187

Jarnagin, W. R., Schwartz, L. H., Gultekin, D. H., Gönen, M., Haviland, D., Shia, J., D'Angelica, M., Fong, Y., DeMatteo, R., Tse, A., Blumgart, L. H., & Kemeny, N. (2009). Regional chemotherapy for unresectable primary liver cancer: Results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. Annals of Oncology, 20(9). https://doi.org/10.1093/annonc/mdp029

Jencks, D. S., Adam, J. D., Borum, M. L., Koh, J. M., Stephen, S., & Doman, D. B. (2018). Overview of current concepts in gastric intestinal metaplasia and gastric cancer. Gastroenterology and Hepatology, 14(2).

Jennings, R. E., Berry, A. A., Strutt, J. P., Gerrard, D. T., & Hanley, N. A. (2015). Human pancreas development. In

Development (Cambridge) (Vol. 142, Issue 18). https://doi.org/10.1242/dev.120063

Joshi, S. S., & Badgwell, B. D. (2021). Current treatment and recent progress in gastric cancer. CA: A Cancer Journal for Clinicians, 71(3). https://doi.org/10.3322/caac.21657

Kamisawa, T., Wood, L. D., Itoi, T., & Takaori, K. (2016). Pancreatic cancer. In The Lancet (Vol. 388, Issue 10039). https://doi.org/10.1016/S0140-6736(16)00141-0

Karabulut, S., Karabulut, M., & Taşteki˙n, D. (2021). WHAT'S NEW IN METASTATIC COLON CANCER TREATMENT? In Istanbul Tip Fakultesi Dergisi (Vol. 84, Issue 3, pp. 425–429). Istanbul University Press. https://doi.org/10.26650/IUITFD.2020.0086

Kaseb, A. O., Shindoh, J., Patt, Y. Z., Roses, R. E., Zimmitti, G., Lozano, R. D., Hassan, M. M., Hassabo, H. M., Curley, S. A., Aloia, T. A., Abbruzzese, J. L., & Vauthey, J. N. (2013). Modified cisplatin/interferon α-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. Cancer, 119(18). https://doi.org/10.1002/cncr.28209

Kilic, L., Ordu, C., Yildiz, I., Sen, F., Keskin, S., Ciftci, R., & Pilanci, K. N. (2016). Current Adjuvant Treatment Modalities For Gastric Cancer: From History to the Future.

World Journal of Gastrointestinal Oncology, 8(5). https://doi.org/10.4251/wjgo.v8.i5.439

Kim, D. W., Talati, C., & Kim, R. (2017). Hepatocellular carcinoma (HCC): Beyond sorafenib-chemotherapy. In Journal of Gastrointestinal Oncology (Vol. 8, Issue 2). https://doi.org/10.21037/jgo.2016.09.07

Kleeff, J., Korc, M., Apte, M., La Vecchia, C., Johnson, C. D., Biankin, A. V., Neale, R. E., Tempero, M., Tuveson, D. A., Hruban, R. H., & Neoptolemos, J. P. (2016). Pancreatic cancer. Nature Reviews Disease Primers, 2. https://doi.org/10.1038/nrdp.2016.22

Ko, Y.-J., Atkins, M. B., & Address, †. (2005). Chemotherapies and Immunotherapies for Metastatic Kidney Cancer.

Kobayakawa, M., & Kojima, Y. (2011). Tegafur/gimeracil/oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: A review comparing it with other fluoropyrimidine-based therapies. OncoTargets and Therapy, 4. https://doi.org/10.2147/OTT.S19059

Kobayashi, D., Kodera, Y., Fukushima, R., Morita, M., Fushida, S., Yamashita, N., Yoshikawa, K., Ueda, S., Yabusaki, H., Kusumoto, T., Arigami, T., Hidemura, A., Omori, T., Yamaguchi, H., Hirono, Y., Tsuji, Y., Moon, J. H., Tomita, T., Imamura, H., … Kitayama, J. (2024). Phase II Study of Intraperitoneal Administration of Paclitaxel Combined with S-1 and Cisplatin for Gastric Cancer with Peritoneal

Metastasis. Annals of Surgical Oncology, 31(2), 735–743. https://doi.org/10.1245/s10434-023-14240-6

Koemans, W. J., Van Der Kaaij, R. T., Boot, H., Buffart, T., Veenhof, A. A. F. A., Hartemink, K. J., Grootscholten, C., Snaebjornsson, P., Retel, V. P., Van Tinteren, H., Vanhoutvin, S., Van Der Noort, V., Houwink, A., Hahn, C., Huitema, A. D. R., Lahaye, M., Los, M., Van Den Barselaar, P., Imhof, O., … Van Sandick, J. W. (2019). Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). BMC Cancer, 19(1). https://doi.org/10.1186/s12885-019-5640-2

Kokova, V. (n.d.). METHODS FOR DETERMINING SUB-ACUTE, SUB-CHRONIC, AND CHRONIC TOXICITY OF CHEMICAL COMPOUNDS. In KNOWLEDGE-International Journal (Vol. 59, Issue 4).

Kontomanolis, E. N., Koutras, A., Syllaios, A., Schizas, D., Mastoraki, A., Garmpis, N., Diakosavvas, M., Angelou, K., Tsatsaris, G., Pagkalos, A., Ntounis, T., & Fasoulakis, Z. (2020). Role of oncogenes and tumor-suppressor genes in carcinogenesis: A review. In Anticancer Research (Vol. 40, Issue 11, pp. 6009–6015). International Institute of Anticancer Research. https://doi.org/10.21873/anticanres.14622

Kosumi, K., Mima, K., Baba, H., & Ogino, S. (2018). Dysbiosis of the gut microbiota and colorectal cancer: the key target of molecular pathological epidemiology. Journal of Laboratory and Precision Medicine, 3. https://doi.org/10.21037/jlpm.2018.09.05

Kretschmer, M., Rüdiger, D., & Zahler, S. (2021). Mechanical aspects of angiogenesis. In Cancers (Vol. 13, Issue 19). https://doi.org/10.3390/cancers13194987

Krump, N. A., & You, J. (2018). Molecular mechanisms of viral oncogenesis in humans. In Nature Reviews Microbiology (Vol. 16, Issue 11, pp. 684–698). Nature Publishing Group. https://doi.org/10.1038/s41579-018-0064-6

Labianca, R., Beretta, G. D., Kildani, B., Milesi, L., Merlin, F., Mosconi, S., Pessi, M. A., Prochilo, T., Quadri, A., Gatta, G., de Braud, F., & Wils, J. (2010). Colon cancer. In Critical Reviews in Oncology/Hematology (Vol. 74, Issue 2, pp. 106–133). https://doi.org/10.1016/j.critrevonc.2010.01.010

Langley, R. R., & Fidler, I. J. (2007). Tumor cell-organ microenvironment interactions in the pathogenesis of cancer metastasis. In Endocrine Reviews (Vol. 28, Issue 3, pp. 297–321). https://doi.org/10.1210/er.2006-0027

Langman, L. J., & Kapur, B. M. (2006). Toxicology: Then and now. Clinical Biochemistry, 39(5). https://doi.org/10.1016/j.clinbiochem.2006.03.004

Lehmann, F., & Wennerberg, J. (2021). Evolution of nitrogen-based alkylating anticancer agents. In Processes (Vol. 9, Issue 2, pp. 1–10). MDPI AG. https://doi.org/10.3390/pr9020377

Lehouritis, P., Cummins, J., Stanton, M., Murphy, C. T., McCarthy, F. O., Reid, G., Urbaniak, C., Byrne, W. L., & Tangney, M. (2015). Local bacteria affect the efficacy of chemotherapeutic drugs. Scientific Reports, 5. https://doi.org/10.1038/srep14554

Lewis, S. M., Williams, A., & Eisenbarth, S. C. (2019). Structure and function of the immune system in the spleen. In Science Immunology (Vol. 4, Issue 33). https://doi.org/10.1126/sciimmunol.aau6085

Li, X., Huang, D. bing, Zhang, Q., Guo, C. xiang, Fu, Q. han, Zhang, X. chen, Tang, T. Y., Su, W., Chen, Y. W., Chen, W., Ma, T., Gao, S. L., Que, R. S., Bai, X. L., & Liang, T. B. (2020). The efficacy and toxicity of chemotherapy in the elderly with advanced pancreatic cancer. Pancreatology, 20(1). https://doi.org/10.1016/j.pan.2019.11.012

Li, X., Ramadori, P., Pfister, D., Seehawer, M., Zender, L., & Heikenwalder, M. (2021). The immunological and metabolic landscape in primary and metastatic liver cancer. In Nature Reviews Cancer (Vol. 21, Issue 9). https://doi.org/10.1038/s41568-021-00383-9

Liang, X., Wu, Q., Luan, S., Yin, Z., He, C., Yin, L., Zou, Y., Yuan, Z., Li, L., Song, X., He, M., Lv, C., & Zhang, W. (2019). A

comprehensive review of topoisomerase inhibitors as anticancer agents in the past decade. In European Journal of Medicinal Chemistry (Vol. 171). https://doi.org/10.1016/j.ejmech.2019.03.034

Lilleby, W., & Fosså, S. D. (2005). Chemotherapy in metastatic renal cell cancer. World Journal of Urology, 23(3). https://doi.org/10.1007/s00345-004-0469-x

Linehan, W. M., & Zbar, B. (2004). Focus on kidney cancer. In Cancer Cell (Vol. 6, Issue 3). https://doi.org/10.1016/j.ccr.2004.09.006

Liu, Y. P., Zheng, C. C., Huang, Y. N., He, M. L., Xu, W. W., & Li, B. (2021). Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. In MedComm (Vol. 2, Issue 3). https://doi.org/10.1002/mco2.55

Lopez Perez, R., Münz, F., Vidoni, D., Rühle, A., Trinh, T., Sisombath, S., Zou, B., Wuchter, P., Debus, J., Grosu, A. L., Saffrich, R., Huber, P. E., & Nicolay, N. H. (2019). Mesenchymal stem cells preserve their stem cell traits after exposure to antimetabolite chemotherapy. Stem Cell Research, 40. https://doi.org/10.1016/j.scr.2019.101536

Louafi, S., Boige, V., Ducreux, M., Bonyhay, L., Mansourbakht, T., De Baere, T., Asnacios, A., Hannoun, L., Poynard, T., & Taïeb, J. (2007). Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma

(HCC): Results of a phase II study. Cancer, 109(7). https://doi.org/10.1002/cncr.22532

Lundqvist, E. Å., Fujiwara, K., & Seoud, M. (2015). Principles of chemotherapy. International Journal of Gynecology and Obstetrics, 131, S146–S149. https://doi.org/10.1016/j.ijgo.2015.06.011

Ma, M. X., & Bourke, M. J. (2016). Complications of endoscopic polypectomy, endoscopic mucosal resection and endoscopic submucosal dissection in the colon. In Best Practice and Research: Clinical Gastroenterology (Vol. 30, Issue 5). https://doi.org/10.1016/j.bpg.2016.09.009

Maehara, Y., Baba, H., & Sugimachi, K. (2001). Adjuvant chemotherapy for gastric cancer: A comprehensive review. In Gastric Cancer (Vol. 4, Issue 4). https://doi.org/10.1007/s10120-001-8008-6

Malki, A., Elruz, R. A., Gupta, I., Allouch, A., Vranic, S., & Al Moustafa, A. E. (2021). Molecular mechanisms of colon cancer progression and metastasis: Recent insights and advancements. In International Journal of Molecular Sciences (Vol. 22, Issue 1). https://doi.org/10.3390/ijms22010130

Maly, J., & Alinari, L. (2016). Pembrolizumab in classical Hodgkin's lymphoma. In European Journal of Haematology (Vol. 97, Issue 3). https://doi.org/10.1111/ejh.12770

Marin, J. J. G., Briz, O., Herraez, E., Lozano, E., Asensio, M., Di Giacomo, S., Romero, M. R., Osorio-Padilla, L. M., Santos-Llamas, A. I., Serrano, M. A., Armengol, C., Efferth, T., & Macias, R. I. R. (2018). Molecular bases of the poor response of liver cancer to chemotherapy. In Clinics and Research in Hepatology and Gastroenterology (Vol. 42, Issue 3). https://doi.org/10.1016/j.clinre.2017.12.006

Markowitz, S. D., Dawson, D. M., Willis, J., & Willson, J. K. V. (2002). Focus on colon cancer. In CELL PRESS (Vol. 1).

McCarten, K. M., Nadel, H. R., Shulkin, B. L., & Cho, S. Y. (2019). Imaging for diagnosis, staging and response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma. In Pediatric Radiology (Vol. 49, Issue 11). https://doi.org/10.1007/s00247-019-04529-8

McKnight, J. A. (2003). Principles of chemotherapy. Clinical Techniques in Small Animal Practice, 18(2). https://doi.org/10.1053/svms.2003.36617

Mebius, R. E., & Kraal, G. (2005). Structure and function of the spleen. In Nature Reviews Immunology (Vol. 5, Issue 8). https://doi.org/10.1038/nri1669

Meng, L., Yang, L., Zhao, X., Zhang, L., Zhu, H., Liu, C., & Tan, W. (2012). Targeted delivery of chemotherapy agents using a liver cancer-specific aptamer. PloS One, 7(4). https://doi.org/10.1371/journal.pone.0033434

Merchant, S. J., Kong, W., Brundage, M., & Booth, C. M. (2021). Symptom Evolution in Patients with Esophageal and Gastric Cancer Receiving Palliative Chemotherapy: A Population-Based Study. Annals of Surgical Oncology, 28(1). https://doi.org/10.1245/s10434-020-09289-6

Meza-Junco, J., Au, H. J., & Sawyer, M. B. (2011). Critical appraisal of trastuzumab in treatment of advanced stomach cancer. In Cancer Management and Research (Vol. 3, Issue 1). https://doi.org/10.2147/CMR.S12698

Midgley, R. S. J. (2000). ABC of colorectal cancer: Adjuvant therapy. BMJ, 321(7270). https://doi.org/10.1136/bmj.321.7270.1208

Milosevic, R., Todorovic, M., Balint, B., Jevtic, M., Krstic, M., Ristanovic, E., Antonijevic, N., Pavlovic, M., Perunicic, M., Petrovic, M., & Mihaljevic, B. (2009). Splenectomy with chemotherapy vs surgery alone as initial treatment for splenic marginal zone lymphoma. World Journal of Gastroenterology, 15(32). https://doi.org/10.3748/wjg.15.4009

Mohamed, A., Menon, H., Chulkina, M., Yee, N. S., & Pinchuk, I. V. (2021). Drug–microbiota interaction in colon cancer therapy: Impact of antibiotics. In Biomedicines (Vol. 9, Issue 3). https://doi.org/10.3390/biomedicines9030259

Morana, O., Wood, W., & Gregory, C. D. (2022). The Apoptosis Paradox in Cancer. In International Journal of Molecular

Sciences (Vol. 23, Issue 3). https://doi.org/10.3390/ijms23031328

Mückter, H. (2003). What is toxicology and how does toxicity occur? Best Practice and Research: Clinical Anaesthesiology, 17(1). https://doi.org/10.1053/bean.2003.0270

Muller, P. Y., & Milton, M. N. (2012). The determination and interpretation of the therapeutic index in drug development. In Nature Reviews Drug Discovery (Vol. 11, Issue 10). https://doi.org/10.1038/nrd3801

Musteata, V. G., Corcimaru, I. T., Iacovleva, I. A., Musteata, L. Z., Suharschii, I. S., & Antoci, L. T. (2004). Treatment options for primary splenic low-grade non-Hodgkin's lymphomas. Clinical and Laboratory Haematology, 26(6). https://doi.org/10.1111/j.1365-2257.2004.00641.x

Nagini, S. (2012). Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World Journal of Gastrointestinal Oncology, 4(7). https://doi.org/10.4251/wjgo.v4.i7.156

Nasir, M. U., Zubair, M., Ghazal, T. M., Khan, M. F., Ahmad, M., Rahman, A. U., Hamadi, H. Al, Khan, M. A., & Mansoor, W. (2022). Kidney Cancer Prediction Empowered with Blockchain Security Using Transfer Learning. Sensors, 22(19). https://doi.org/10.3390/s22197483

Nitiss, J. L. (2009). Targeting DNA topoisomerase II in cancer chemotherapy. In Nature Reviews Cancer (Vol. 9, Issue 5). https://doi.org/10.1038/nrc2607

Nygren, P. (2001). What is cancer chemotherapy? Acta Oncologica, 40(2–3). https://doi.org/10.1080/02841860117342

Ogawa, M. (1997). Anticancer drugs and pharmacologic actions. In Nippon rinsho. Japanese journal of clinical medicine (Vol. 55, Issue 5).

Okamoto, Y., Kanzaki, H., Tanaka, T., Sakae, H., Abe, M., Iwamuro, M., Kawano, S., Kawahara, Y., & Okada, H. (2021). Gastric Adenoma: A High Incidence Rate of Developing Carcinoma and Risk of Metachronous Gastric Cancer according to Long-Term Follow-Up. Digestion, 102(6). https://doi.org/10.1159/000515213

Okazaki, T., Javle, M., Tanaka, M., Abbruzzese, J. L., & Li, D. (2010). Single nucleotide polymorphisms of gemcitabine metabolic genes and pancreatic cancer survival and drug toxicity. Clinical Cancer Research, 16(1). https://doi.org/10.1158/1078-0432.CCR-09-1555

Orcutt, S. T., & Anaya, D. A. (2018). Liver resection and surgical strategies for management of primary liver cancer. In Cancer Control (Vol. 25, Issue 1). https://doi.org/10.1177/1073274817744621

Ouyang, D. L., Chen, J. J., Getzenberg, R. H., & Schoen, R. E. (2005). Noninvasive testing for colorectal cancer: A

review. In American Journal of Gastroenterology (Vol. 100, Issue 6). https://doi.org/10.1111/j.1572-0241.2005.41427.x

Owumi, S. E., Adebisi, G. E., & Odunola, O. A. (2023). Epirubicin toxicity in rat's ovary and uterus: A protective role of 3-Indolepropionic acid supplementation. Chemico-Biological Interactions, 374. https://doi.org/10.1016/j.cbi.2023.110414

Padrón, L. J., Maurer, D. M., O'Hara, M. H., O'Reilly, E. M., Wolff, R. A., Wainberg, Z. A., Ko, A. H., Fisher, G., Rahma, O., Lyman, J. P., Cabanski, C. R., Yu, J. X., Pfeiffer, S. M., Spasic, M., Xu, J., Gherardini, P. F., Karakunnel, J., Mick, R., Alanio, C., … Vonderheide, R. H. (2022). Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial. Nature Medicine, 28(6). https://doi.org/10.1038/s41591-022-01829-9

Palmela, C., Velho, S., Agostinho, L., Branco, F., Santos, M., Santos, M. P. C., Oliveira, M. H., Strecht, J., Maio, R., Cravo, M., & Baracos, V. E. (2017). Body composition as a prognostic factor of neoadjuvant chemotherapy toxicity and outcome in patients with locally advanced gastric cancer. Journal of Gastric Cancer, 17(1). https://doi.org/10.5230/jgc.2017.17.e8

Pascual, D., & Borque, A. (2008). Epidemiology of Kidney Cancer. Advances in Urology, 2008. https://doi.org/10.1155/2008/782381

Patel, A. K. (2012). The Cell Biological Basis of Cancer.

Petit, K., Suwalsky, M., Colina, J. R., Contreras, D., Aguilar, L. F., Jemiola-Rzeminska, M., & Strzalka, K. (2020). Toxic effects of the anticancer drug epirubicin in vitro assayed in human erythrocytes. Toxicology in Vitro, 68. https://doi.org/10.1016/j.tiv.2020.104964

Pollet, R. M., D'Agostino, E. H., Walton, W. G., Xu, Y., Little, M. S., Biernat, K. A., Pellock, S. J., Patterson, L. M., Creekmore, B. C., Isenberg, H. N., Bahethi, R. R., Bhatt, A. P., Liu, J., Gharaibeh, R. Z., & Redinbo, M. R. (2017). An Atlas of β-Glucuronidases in the Human Intestinal Microbiome. Structure, 25(7). https://doi.org/10.1016/j.str.2017.05.003

Poordad, F. F. (2015). Presentation and complications associated with cirrhosis of the liver. In Current Medical Research and Opinion (Vol. 31, Issue 5). https://doi.org/10.1185/03007995.2015.1021905

Poorolajal, J., Moradi, L., Mohammadi, Y., Cheraghi, Z., & Gohari-Ensaf, F. (2020). Risk factors for stomach cancer: a systematic review and meta-analysis. In Epidemiology and Health (Vol. 42). https://doi.org/10.4178/epih.e2020004

Postel-Vinay, S., Collette, L., Paoletti, X., Rizzo, E., Massard, C., Olmos, D., Fowst, C., Levy, B., Mancini, P., Lacombe, D., Ivy, P., Seymour, L., Le Tourneau, C., Siu, L. L., Kaye, S. B., Verweij, J., & Soria, J. C. (2014). Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents - Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies, an European Organisation for Research and Treatment of Cancer-led study. European Journal of Cancer, 50(12). https://doi.org/10.1016/j.ejca.2014.04.031

Power, D. G., & Kemeny, N. E. (2009). The role of floxuridine in metastatic liver disease. Molecular Cancer Therapeutics, 8(5). https://doi.org/10.1158/1535-7163.MCT-08-0709

Qin, A. (2023). An anti-cancer surveillance by the interplay between interferon-beta and retinoblastoma protein RB1. In Frontiers in Oncology (Vol. 13). Frontiers Media S.A. https://doi.org/10.3389/fonc.2023.1173467

Radulescu, L. M., Radulescu, D., Ciuleanu, T. E., Crisan, D., Buzdugan, E., Romitan, D. M., & Buzoianu, A. D. (2021). Cardiotoxicity associated with chemotherapy used in gastrointestinal tumours. In Medicina (Lithuania) (Vol. 57, Issue 8). https://doi.org/10.3390/medicina57080806

Rajapaksha, I. (2022). Liver Fibrosis, Liver Cancer, and Advances in Therapeutic Approaches. In Livers (Vol. 2, Issue 4). https://doi.org/10.3390/livers2040028

Reddy, K. B. (2015). MicroRNA (miRNA) in cancer. In Cancer Cell International (Vol. 15, Issue 1). https://doi.org/10.1186/s12935-015-0185-1

Reis, C. A., David, L., Correa, P., Carneiro, F., De Bolós, C., Garcia, E., Mandel, U., Clausen, H., & Sobrinho-Simões, M. (1999). Intestinal metaplasia of human stomach displays distinct patterns of mucin (MUC1, MUC2, MUC5AC, and MUC6) expression. Cancer Research, 59(5).

Rex, D. K., Johnson, D. A., Anderson, J. C., Schoenfeld, P. S., Burke, C. A., & Inadomi, J. M. (2009). American college of gastroenterology guidelines for colorectal cancer screening 2008. In American Journal of Gastroenterology (Vol. 104, Issue 3). https://doi.org/10.1038/ajg.2009.104

Rivera, F., Vega-Villegas, M. E., & López-Brea, M. F. (2007). Chemotherapy of advanced gastric cancer. In Cancer Treatment Reviews (Vol. 33, Issue 4, pp. 315–324). https://doi.org/10.1016/j.ctrv.2007.01.004

Rozman, K. K., & Doull, J. (2000). Dose and time as variables of toxicity. Toxicology, 144(1–3). https://doi.org/10.1016/S0300-483X(99)00204-8

Rühle, A., Huber, P. E., Saffrich, R., Lopez Perez, R., & Nicolay, N. H. (2018). The current understanding of mesenchymal

stem cells as potential attenuators of chemotherapy-induced toxicity. In International Journal of Cancer (Vol. 143, Issue 11). https://doi.org/10.1002/ijc.31619

Sahora, K., Kuehrer, I., Schindl, M., Koelblinger, C., Goetzinger, P., & Gnant, M. (2011). NeoGemTax: Gemcitabine and Docetaxel as Neoadjuvant Treatment for Locally Advanced Nonmetastasized Pancreatic Cancer. World Journal of Surgery, 35(7). https://doi.org/10.1007/s00268-011-1113-8

Sancho, E., Batlle, E., & Clevers, H. (2004). Signaling pathways in intestinal development and cancer. In Annual Review of Cell and Developmental Biology (Vol. 20). https://doi.org/10.1146/annurev.cellbio.20.010403.092805

Saung, M. T., & Zheng, L. (2017). Current Standards of Chemotherapy for Pancreatic Cancer. In Clinical Therapeutics (Vol. 39, Issue 11). https://doi.org/10.1016/j.clinthera.2017.08.015

Scelo, G., & Larose, T. L. (2018). Epidemiology and risk factors for kidney cancer. In Journal of Clinical Oncology (Vol. 36, Issue 36). https://doi.org/10.1200/JCO.2018.79.1905

Schneiderman, M. A., Myers, M. H., Sathe, Y. S., & Koffsky, P. (1964). Toxicity, the therapeutic index, and the ranking of drugs. Science, 144(3623). https://doi.org/10.1126/science.144.3623.1212

Schoen, R. E. (2002). The case for population-based screening for colorectal cancer. In Nature Reviews Cancer (Vol. 2, Issue 1). https://doi.org/10.1038/nrc705

Sears, C. L., Geis, A. L., & Housseau, F. (2014). Bacteroides fragilis subverts mucosal biology: From symbiont to colon carcinogenesis. In Journal of Clinical Investigation (Vol. 124, Issue 10). https://doi.org/10.1172/JCI72334

Shankar, V., Gilmore, M. S., Elkins, R. C., & Sachdev, G. P. (1994). A novel human airway mucin cDNA encodes a protein with unique tandem-repeat organization. Biochemical Journal, 300(2). https://doi.org/10.1042/bj3000295

Singh, K. E., Taylor, T. H., Pan, C.-J. G., Stamos, M. J., & Zell, J. A. (2014). Colorectal Cancer Incidence Among Young Adults in California. Journal of Adolescent and Young Adult Oncology, 3(4). https://doi.org/10.1089/jayao.2014.0006

Skok, Ž., Zidar, N., Kikelj, D., & Ilaš, J. (2020). Dual Inhibitors of Human DNA Topoisomerase II and Other Cancer-Related Targets. In Journal of Medicinal Chemistry (Vol. 63, Issue 3). https://doi.org/10.1021/acs.jmedchem.9b00726

Slagter, A. E., Tudela, B., van Amelsfoort, R. M., Sikorska, K., van Sandick, J. W., van de Velde, C. J. H., van Grieken, N. C. T., Lind, P., Nordsmark, M., Putter, H., Hulshof, M. C. C. M., van Laarhoven, H. W. M., Grootscholten, C., Braak, J. P. B. M., Meershoek-Klein Kranenbarg, E., Jansen, E. P.

M., Cats, A., & Verheij, M. (2020). Older versus younger adults with gastric cancer receiving perioperative treatment: Results from the CRITICS trial. European Journal of Cancer, 130. https://doi.org/10.1016/j.ejca.2020.02.008

Smith, R. A., von Eschenbach, A. C., Wender, R., Levin, B., Byers, T., Rothenberger, D., Brooks, D., Creasman, W., Cohen, C., Runowicz, C., Saslow, D., Cokkinides, V., & Eyre, H. (2001). American Cancer Society Guidelines for the Early Detection of Cancer: Update of Early Detection Guidelines for Prostate, Colorectal, and Endometrial Cancers: ALSO: Update 2001--Testing for Early Lung Cancer Detection. CA: A Cancer Journal for Clinicians, 51(1). https://doi.org/10.3322/canjclin.51.1.38

Soveri, L. M., Lamminmäki, A., Hänninen, U. A., Karhunen, M., Bono, P., & Osterlund, P. (2019). Long-term neuropathy and quality of life in colorectal cancer patients treated with oxaliplatin containing adjuvant chemotherapy. Acta Oncologica, 58(4). https://doi.org/10.1080/0284186X.2018.1556804

Srivatanakul, P., Sriplung, H., & Deerasamee, S. (2004). Epidemiology of liver cancer: An overview. Asian Pacific Journal of Cancer Prevention, 5(2).

Sugarbaker, P. H. (2021). Intraperitoneal paclitaxel: Pharmacology, clinical results and future prospects. In

Journal of Gastrointestinal Oncology (Vol. 12). https://doi.org/10.21037/JGO-2020-03

Sun, B., & Karin, M. (2012). Obesity, inflammation, and liver cancer. In Journal of Hepatology (Vol. 56, Issue 3). https://doi.org/10.1016/j.jhep.2011.09.020

Sun, S., Yan, H., Chen, G., Yang, S., Wang, J., Yang, Y., & Wang, H. (2022). Use of Lentinan and Fluopimomide to Control Cotton Seedling Damping-Off Disease Caused by Rhizoctonia solani. Agriculture (Switzerland), 12(1). https://doi.org/10.3390/agriculture12010075

Sun, Y., Liu, Y., Ma, X., & Hu, H. (2021). The influence of cell cycle regulation on chemotherapy. In International Journal of Molecular Sciences (Vol. 22, Issue 13). https://doi.org/10.3390/ijms22136923

Taieb, J., & Gallois, C. (2020). Adjuvant chemotherapy for stage iii colon cancer. In Cancers (Vol. 12, Issue 9). https://doi.org/10.3390/cancers12092679

Tam, K. (2013). The roles of doxorubicin in hepatocellular carcinoma. In ADMET and DMPK (Vol. 1, Issue 3). https://doi.org/10.5599/admet.1.3.7

Tannir, N. M., Thall, P. F., Ng, C. S., Wang, X., Wooten, L., Siefker-Radtke, A., Mathew, P., Pagliaro, L., Wood, C., & Jonasch, E. (2008). A Phase II Trial of Gemcitabine Plus Capecitabine for Metastatic Renal Cell Cancer Previously Treated With Immunotherapy and Targeted Agents.

Journal of Urology, 180(3). https://doi.org/10.1016/j.juro.2008.05.017

Terzić, J., Grivennikov, S., Karin, E., & Karin, M. (2010). Inflammation and Colon Cancer. Gastroenterology, 138(6). https://doi.org/10.1053/j.gastro.2010.01.058

Thakur, A., & Jain, S. K. (2011). Kidney Cancer: Current Progress in Treatment. World Journal of Oncology, 2(4). https://doi.org/10.4021/wjon345w

Tobelem, G. (2007). VEGF: A key therapeutic target for the treatment of cancer-insights into its role and pharmacological inhibition. Targeted Oncology, 2(3). https://doi.org/10.1007/s11523-007-0051-8

Tsaioun, K., Blaauboer, B. J., & Hartung, T. (2016). Evidence-based absorption, distribution, metabolism, excretion (ADME) and its interplay with alternative toxicity methods. Altex, 33(4), 343–358. https://doi.org/10.14573/altex.1610101

Vallon, V., Mühlbauer, B., & Osswald, H. (2006). Adenosine and kidney function. In Physiological Reviews (Vol. 86, Issue 3). https://doi.org/10.1152/physrev.00031.2005

Vichaya, E. G., Chiu, G. S., Krukowski, K., Lacourt, T. E., Kavelaars, A., Dantzer, R., Heijnen, C. J., & Walker, A. K. (2015). Mechanisms of chemotherapy-induced behavioral toxicities. In Frontiers in Neuroscience (Vol. 9, Issue APR). https://doi.org/10.3389/fnins.2015.00131

Visone, R., & Croce, C. M. (2009). MiRNAs and cancer. American Journal of Pathology, 174(4). https://doi.org/10.2353/ajpath.2009.080794

V.J., P., R.A., A., P.A., D., W., T., E.M., O., E., G., R.C., M., L.S., W., M.L., R., & M.C., P. (2011). Multicenter phase II trial of adjuvant therapy for resected pancreatic cancer using cisplatin, 5-fluorouracil, and interferon-alfa-2b-based chemoradiation: ACOSOG Trial Z05031. In Annals of Oncology (Vol. 22, Issue 2).

Vodenkova, S., Buchler, T., Cervena, K., Veskrnova, V., Vodicka, P., & Vymetalkova, V. (2020). 5-fluorouracil and other fluoropyrimidines in colorectal cancer: Past, present and future. In Pharmacology and Therapeutics (Vol. 206). https://doi.org/10.1016/j.pharmthera.2019.107447

Wang, T., Dong, J., Zhang, Y., Ren, Z., Liu, Y., Yang, X., Sun, D., & Wang, Y. (2022). Efficacy and safety of hepatic artery infusion chemotherapy with mFOLFOX in primary liver cancer patients with hyperbilirubinemia and ineffective drainage: a retrospective cohort study. Annals of Translational Medicine, 10(7). https://doi.org/10.21037/atm-22-978

Was, H., Borkowska, A., Bagues, A., Tu, L., Liu, J. Y. H., Lu, Z., Rudd, J. A., Nurgali, K., & Abalo, R. (2022). Mechanisms of Chemotherapy-Induced Neurotoxicity. In Frontiers in Pharmacology (Vol. 13). https://doi.org/10.3389/fphar.2022.750507

Wheelwright, M., Spartz, E. J., Skubitz, K., Yousaf, H., Murugan, P., & Harmon, J. V. (2021). Primary angiosarcoma of the spleen, a rare indication for splenectomy: a case report. International Journal of Surgery Case Reports, 82. https://doi.org/10.1016/j.ijscr.2021.105929

Wilson, N. R., Wiele, A. J., Surasi, D. S., Rao, P., Sircar, K., Tamboli, P., Shah, A. Y., Genovese, G., Karam, J. A., Wood, C. G., Tannir, N. M., & Msaouel, P. (2021). Efficacy and safety of gemcitabine plus doxorubicin in patients with renal medullary carcinoma. Clinical Genitourinary Cancer, 19(6). https://doi.org/10.1016/j.clgc.2021.08.007

Wolf, A., Fontham, E. T., Church, T. R., Flowers, C. R., Guerra, C. E., LaMonte, S. J., Etzioni, R., McKenna, M. T., Oeffinger, K. C., Tina Shih, Y.-C., Walter, L. C., Andrews, K. S., Brawley, O. W., Brooks, D., Fedewa, S. A., Manassaram-Baptiste, D., Siegel, R. L., Wender, R. C., Smith, R. A., … D Wolf, A. M. (2018). Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society; 6 Independent retired physician and patient advocate. CA: A Cancer Journal for Clinicians CA CANCER J CLIN, 68.

Wolf, A. M. D., Fontham, E. T. H., Church, T. R., Flowers, C. R., Guerra, C. E., LaMonte, S. J., Etzioni, R., McKenna, M. T., Oeffinger, K. C., Shih, Y. T., Walter, L. C., Andrews, K. S., Brawley, O. W., Brooks, D., Fedewa, S. A., Manassaram-Baptiste, D., Siegel, R. L., Wender, R. C., & Smith, R. A.

(2018). Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA: A Cancer Journal for Clinicians, 68(4). https://doi.org/10.3322/caac.21457

Wrobel, P., & Ahmed, S. (2019). Current status of immunotherapy in metastatic colorectal cancer. In International Journal of Colorectal Disease (Vol. 34, Issue 1). https://doi.org/10.1007/s00384-018-3202-8

Wu, C., Wang, N., Zhou, H., Wang, T., Mao, Q., Zhang, X., & Zhao, D. (2020). Effects of Neoadjuvant Chemotherapy Toxicity and Postoperative Complications on Short-term and Long-term Outcomes After Curative Resection of Gastric Cancer. Journal of Gastrointestinal Surgery, 24(6). https://doi.org/10.1007/s11605-019-04257-2

Yahya, F. A., Hashim, N. F. M., Israf Ali, D. A., Chau Ling, T., & Cheema, M. S. (2021). A brief overview to systems biology in toxicology: The journey from in to vivo, in-vitro and –omics. In Journal of King Saud University - Science (Vol. 33, Issue 1). https://doi.org/10.1016/j.jksus.2020.101254

Yang, Y. M., Kim, S. Y., & Seki, E. (2019). Inflammation and Liver Cancer: Molecular Mechanisms and Therapeutic Targets. Seminars in Liver Disease, 39(1). https://doi.org/10.1055/s-0038-1676806

Ye, X., Wang, A., Lin, W., Xu, Y., Dong, X., Zhou, Y., Tian, K., & Xu, X. (2022). The Role of Intestinal Flora in Anti-Tumor

Antibiotic Therapy. Frontiers in Bioscience - Landmark, 27(10). https://doi.org/10.31083/j.fbl2710281

Ying, J. E., Zhu, L. M., & Liu, B. X. (2012). Developments in metastatic pancreatic cancer: Is gemcitabine still the standard? World Journal of Gastroenterology, 18(8). https://doi.org/10.3748/wjg.v18.i8.736

Yu, J., Gao, Y., Chen, L., Wu, D., Shen, Q., Zhao, Z., Liu, W., Yang, H., Zhang, Q., Wang, X., Hu, P., Zheng, Z., Wang, X., Liu, H., Xu, Z., Yan, Z., Wu, Y., Jin, M., Zhang, Q., … Shou, C. (2022). Effect of S-1 Plus Oxaliplatin Compared with Fluorouracil, Leucovorin Plus Oxaliplatin as Perioperative Chemotherapy for Locally Advanced, Resectable Gastric Cancer: A Randomized Clinical Trial. JAMA Network Open. https://doi.org/10.1001/jamanetworkopen.2022.0426

Zahrani, K. A., Judaibi, E. A., Khayyat, S. A., Galal, K., & Alrashedi, M. (2019). Influence of Chemotherapy Treatment on Escherichia coli. In International Journal of Cancer and Treatment (Vol. 2, Issue 1). www.innovationinfo.org

Zhang, X., Chen, H., Lu, Y., Xu, C., Yao, W., Xu, L., Zhang, R., Zhang, L., & Yao, Q. (2020). Prevention of oxaliplatin-related neurotoxicity by ω-3 PUFAs. Medicine, 99(50). https://doi.org/10.1097/md.0000000000023564

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