CHAPTER 15

The Hidden Costs of Healing: Organ Damages in Cancer Treatments

MEHRAB KHALIL[1], AMNA TAHIR[1], MARYAM JAVED[1], RIDA AZAM[1], MARIUM JAMEEL[1], HUMA NAZ[2], ALI AKBAR[1*], MUHAMMAD FAISAL HAYAT[1]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2]Department of Zoology, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan
[*]Corresponding author: ali0703593@gmail.com

SUMMARY

Cancer is a complex and devastating disease, instigated by genetic or epigenetic alterations that lead to the uncontrollable growth of cells. Current diagnostic approaches related to cancer include imaging, laboratory tests and morphological analysis which facilitates the accurate identification and classification of cancer types. Treatment strategies associated with cancer involve a combination of modalities related to the specific cancer type, stage, and patient health. Chemotherapy is a keystone in cancer treatment which targets rapidly dividing cells but also poses a challenge as it affects not only cancer cells but also healthy cells. This chapter focuses on the organ damage associated with commonly employed chemotherapeutic agents. Doxorubicin (DOX) is a widely used anthracycline that disrupts DNA replication whereas cisplatin (CP) is a potent DNA alkylating agent that forms DNA cross-links and methotrexate (MTX) is an antimetabolite that inhibits dihydrofolate reductase. All these drugs are used to treat cancer with potential side effects including cardiotoxicity, nephrotoxicity, myelosuppression, and peripheral neuropathy, respectively. Paclitaxel (PTX) stabilizes the microtubules, and tamoxifen (TAM) blocks the estrogen receptors, both play essential roles in cancer therapy with potential side effects including peripheral neuropathy and menopausal symptoms. Letrozole (LTZ) suppresses the estrogen level in hormone-receptor-positive breast cancer, 5-Fluorouracil (5-FU) inhibits DNA synthesis in various solid tumors, Bleomycin (BLM) induces DNA damage in lymphomas and germ cell tumors, and Vincristine (VCT) disrupts microtubules in leukemia and lymphomas, all while potentially causing side effects such as nausea, myelosuppression, pulmonary toxicity, and neuropathy, respectively.

INTRODUCTION

Cancer is an ailment that results from epigenetic or genetic changes in the somatic cells (Saini et al., 2020). These alterations lead to uncontrollable growth and proliferation of cells to form lumps or masses called as tumors (Nenclares & Harrington, 2020). Tumors can be of two types viz. benign or malignant. Benign tumors are usually non-cancerous and do not invade surrounding tissues (Boutry et al., 2022). Malignant tumors are cancerous and can spread in any tissue or organ of the body through the lymphatic system or bloodstream. Moreover, there are hundreds of cancers that are categorized based on the organ in which they originated such as lung, colon, breast, ovary, kidney, head and neck, bladder and many others (Galon et al., 2012).

Cancer cells disturb the hormone levels and harm the digestive, circulatory and nervous systems by altering the body functions (Cheng et al., 2021). Factors such as aging populations, lifestyle changes, and environmental exposures also contribute to the rising incidence of cancer (Madia et al., 2019). A global cancer diagnosis is predicted to rise to ~26 million by 2040, from which 15 million are those cases that require chemotherapy, primarily for colorectal, breast and lung cancers [16.4, 12.7 and 15.0%, respectively (Wilson et al., 2019)]. According to the American Cancer Society (Sung et al., 2021), cancer is the second leading cause of morbidity and mortality worldwide, accounting for 10 million deaths in 2020 (Fig 1).

Modern techniques for diagnosing cancer include imaging techniques, lab examinations, and morphological analysis of cells and tissues, which is typically regarded as extremely reliable in the majority of cancer diagnoses (Zhang et al., 2019). Pathological features that aid in the diagnosis of cancer include histological changes, immunohistochemical (IHC) analysis, mutational and molecular genetics examination (Cryer & Thorley, 2019). The treatment of cancer is a multifaceted approach that often involves a combination of therapies associated to the overall health of the patient, the kind and stage of cancer, and treatment objectives such as control, cure or palliation (Ruggiero et al., 2022). Common treatment modalities include Chemotherapy (chemicals or drugs are used to kill or slow the growth of rapidly dividing cells), Immunotherapy (using medication or other therapies to strengthen the immune system), surgery (surgically removing cancer cells), Precision medicine (recent technique, patient's optimal course of action is selected by genetic testing) and radiation therapy [high doses of radiation to treat cancer (Saini et al., 2020.

How to Cite: Khalil M, A Tahir, M Javed, R Azam, M Jameel, H Naz, A Akbar & MF Hayat, 2024. The Hidden Costs of Healing: Organ damages in Cancer Treatments. In: Zoology: Advancements and Research Trends (Ijaz MU, N Ehsan, M Imran & S Yousaf, eds): FahumSci, Lahore, Pakistan, pp: 114-123. ISBN: 978-627-7745-02-8. https://doi.org/10.61748/Zool.2024/xxx

Chemotherapy is used to eliminate or control the cancer cells, but it can also affect normal, healthy cells that divide quickly, such as those in the bone marrow hair follicles and digestive tract (Kaur et al., 2022). Chemotherapeutic drugs can be administered in various ways, including orally (in the form of pills or capsules), intravenously (through a vein), intramuscularly (into a muscle), or topically [applied to the skin (Neupane et al., 2021)]. Common side effects of chemotherapy may include nausea, vomiting, hair loss, fatigue, and an increased risk of infection due to the impact on the immune system (Roy et al., 2023). Advances in medical research continue to improve the effectiveness and reduce the side effects of chemotherapy, and it is frequently employed alongside various other cancer therapies like surgery, radiation therapy (Nurgali et al., 2018), targeted therapy or immunotherapy (Fig 2).

POTENTIAL CHEMOTHERAPEUTIC DRUGS AND THEIR IMPACT ON BODY ORGANS

Chemotherapy is a treatment that uses drugs to kill cancer cells or stop them from growing and dividing. While chemotherapeutic drugs are designed to target rapidly dividing cells, due to their ability to impact normal, healthy cells in the body, resulting in diverse adverse effects. The impact of chemotherapy drugs on body organs can vary depending on the specific drug, dosage and duration of treatment (Siegel et al., 2018). Here are some drugs that are used in treatment of cancer; Doxorubicin, Cisplatin, Methotrexate, Paclitaxel, Tamoxifen, Letrozole, 5-Fluorouracil, Bleomycin and Vincristine (Table 1).

Doxorubicin (DOX)

The Streptomyces peucetius bacteria produces an antibiotic known as doxorubicin (DOX), which has been extensively utilized as a chemotherapeutic agent since the 1960s. DOX is classified within the group of chemotherapeutic drugs called anthracyclines. It is administered for various cancers including ovarian, breast, bladder, cartilage, thyroid and bone sarcomas, as well as for Hodgkin lymphoma, acute myeloblastic leukemia, small cell lung cancer and acute lymphoblastic leukemia. One of the most effective cancer therapies is chemotherapy, which targets rapidly dividing cells with anti-cancer medications (Punia, et al., 2017). Chemotherapy has an impact on all of the body's rapidly dividing and growing cells. This encompasses both cancer and healthy cells, such as blood cells that multiply in the bone marrow or cells found in the stomach, skin, and reproductive organs (Ayla et al., 2011). In current therapy, the cytotoxicity of chemotherapeutic medications is decreased, and their survival rates are increased by employing numerous combinations of these treatments (Mantawy et al., 2014). Nevertheless, even with the use of these medications at safe dosages, children and young patients who undergo chemotherapy during the prepubertal period may still exhibit permanent damage or a loss of fertility (Coelho et al., 2017). Nowadays, anthracyclines, most commonly doxorubicin (DOX), are administered to about 60% of children diagnosed with cancer among other types of antineoplastic drugs (Siebel et al., 2020).

Antineoplastic medication doxorubicin, or Dox, is used to treat a variety of human cancers, primarily solid tumors (Kumar et al., 2014). Its remarkable effectiveness and extensive positive benefits are credited with its success. However, there are numerous acute and long-term dose-related adverse effects and widespread toxicities linked to its use, such as dysregulation of the digestive tract, degeneration of bone marrow, cardiotoxicity, nephrotoxicity and hepatotoxicity (Wang et al., 2015; Jacevic et al., 2017). Common side effects of DOX include alopecia, fatigue, nausea, oral ulcers and vomiting. It may also lead to bone marrow suppression and increase the risk of developing secondary cancers. Intravenous administration of DOX can result in severe tissue necrosis and ulceration if extravasation occurs. Furthermore, long-term use of DOX is associated with significant cardiac toxicity, leading to restricted usage (Oikonomou et al., 2018).

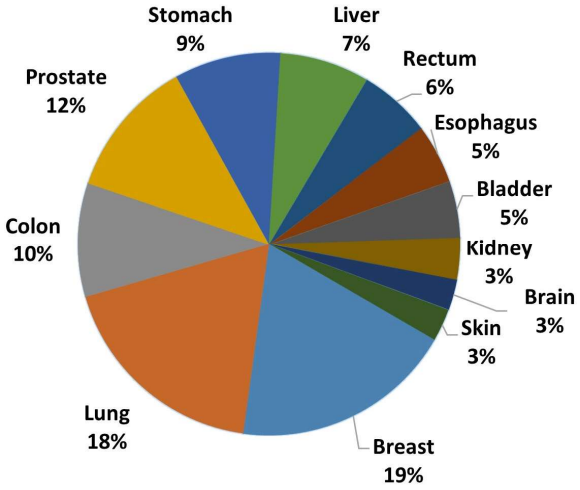

Fig 1. Cancer incidence analysis: 2020

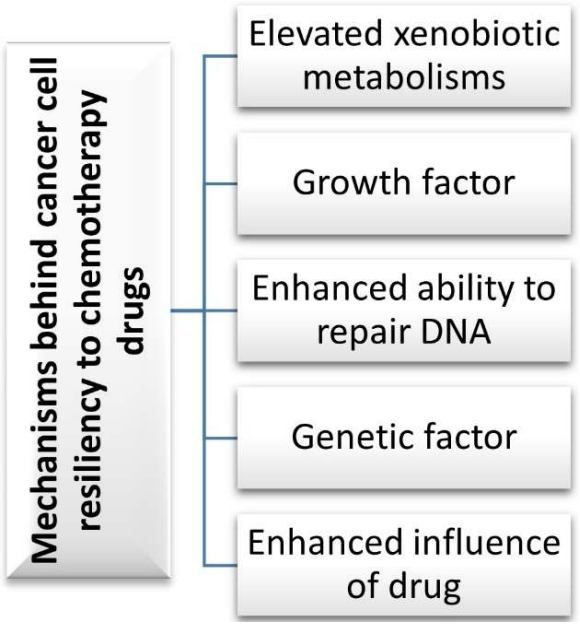

Fig 2. Understanding cancer cell resilience to chemotherapy

One of the most successful and extensively used chemotherapeutic drugs, is doxorubicin (DOX), which is utilized for the treatment of various malignant carcinomas, including sarcomas, Wilm tumors, hematological leukemia, lymphocytic/non-lymphocytic leukemia, and neuroblastoma (Sirwi et al., 2021). In the 1950s, an antibiotic that was derived from a novel strain of Streptomyces paucities that produced a vivid red pigment was found to have effective antitumor action against mice tumors. The novel substance, known by the name daunorubicin, was effectively employed to treat lymphoma and acute leukemia. But by 1967, it was known that daunorubicin might cause cardiac toxicity that proved lethal (Ivanka, 2014).

Doxorubicin's side effects remain a major issue despite its widespread therapeutic use. As a first-line chemotherapeutic medication, either in combination or alone, the doxorubicin medication is still favored for a significant proportion of malignancies. The main detrimental aspects currently include side effects as well as the emergence of chemo resistance. Nonetheless, current studies concentrate on various medication formulations, tailored treatment approaches, and adjuvant therapy for dox in order to efficiently lower the dosage, improve the medication's effectiveness, and lessen its negative effects (Kumar et al., 2014).

Cisplatin (CP)

The development of cancer drugs has changed dramatically from a small-scale, government-funded research project to a multibillion-dollar, high-stakes industry. The limits of chemotherapy that were found by early researchers have been eliminated with the development of focused therapy. Based on their level of toxicity, drugs are categorized into two groups: alkylating agents (like cisplatin and 5-fluorouracil) and inhibitors of deoxyribonucleic acid (DNA) production [like cytosine arabinoside and methotrexate (Henley et al., 2020)].

CP is widely recognized as an efficacious chemotherapeutic medication used to combat diverse malignancies (Ijaz et al., 2020). For many years, cisplatin is considered as a first-line chemotherapy drug to cure a wider range of malignancies (Dasari et al., 2014). The reduction of carcinogenesis and metastasis results in the attenuation of malignancies treated with cisplatin. The average statistics of diseases and mortality, are high (Sung, et al., 2021) which may be the result of long-term use that affects tumor adaptability (Sayyed, et al., 2021), drug efflux (Hong, et al., 2021), or acclimatization in various biochemical (Morelli, et al., 2021) immune network (Graboski, et al., 2021), and pathophysiological disorders with widespread toxicities in the organs instigated by cancer (Razak, et al., 2021).

Basically, CP is a DNA alkylating chemical that breaks double strands and enforces DNA crosslinking to provide its anti-cancerous effects. These CP effects may contribute to disruptions in transcription and DNA replication processes, which would then result in apoptosis (Reddy et al., 2016). CP is categorized as a carcinogenic substance as well since it

Table 1. Various sorts of chemotherapeutic drugs and their fundamental composition

Drugs	Composition	Discovery	Citations
Doxorubicin	It was originally isolated from *Streptomyces peucetius* var. caesius, (the microbe that produces daunorubicin) through mutagenesis treatment of S. peucetius.	It was originally identified in 1969.	Arcamone et al.,1969
Cisplatin	First platinum compound approved by the FDA for use in cancer therapy.	Discovered to possess cytotoxic qualities in the 1960s, recognized as crucial component for the systemic therapy of germ cell malignancies by the late 1970s.	Kelland, 2007
Methotrexate	MTX, which was formerly called amethopterin, is one of the antagonists of folic acid.	First created in the 1940s for the treatment of cancers.	Seeger et al.,1949
Paclitaxel	Paclitaxel was isolated and identified from the bark extract of the Taxus brevifolia, or Pacific Yew Tree.	Under Dr. Jonathan L. Hartwell's direction, the National Cancer Institute launched a screening study in 1960 to find plant extracts having anticancer properties. This program led to the discovery of paclitaxel.	Wani et al., 1971; Wani & Horwitz, 2014
Tamoxifen	The trans isomer of a substituted triphenylethylene that has antiestrogenic properties named as tamoxifen.	Early 1970s, a post-coital contraceptive that didn't work ICI 46,474, reinvented as tamoxifen, was the first targeted treatment for breast cancer.	Bychkovsky et al., 2022
Letrozole			
5-Fluorouracil	5-Fluorouracil (5-FU) is an anti-metabolite that occurs when hydrogen is substituted with fluorine at the C-5 position of uracil.	First manufactured by Heidelberger et al. 60 years ago to utilize the increased uptake of uracil by tumors.	Heidelberger et al., 1957; Vertessy & Toth, 2009
Vincristine	Extracted from *Catharanthus roseus,* natural plant source	Revealed in 1985 and found valuable in curing cancer.	Ravina, 2011
Bleomycin	Isolated from the fermentation broth of *Streptomyces verticillus.*	Drug was discovered in 1962	Umezawa et al., 1966

causes death on its own and generates crosslinks with DNA, which is its main anticancer action. Continuous platinum exposure increased the risk of gastrointestinal tract polyposis in pediatric cancer survivors and elevated the risk of cardiovascular and respiratory diseases, which in particular killed patients with testicular cancer.

Treatment with cisplatin can cause severe nephrotoxicity (Casanova, et al., 2021), which can result in dialysis at last stage; neurotoxicity, which can manifest as the ototoxicity (Kunal, et al., 2021), vestibulopathy (Kobel, et al., 2021), and peripheral neuropathies, which are less common in younger patients. Cardiomyocytes (Albini, et al.,2021), as well as hypertension (Fang, et al., 2021), vascular injury and the metabolic syndrome (Dieckmann et al., 2011), are associated with cardiovascular co-morbidities. The drug's circulating plasma levels can continue for several decades after therapy ceases, which is a drawback of using cisplatin (Gautama, et al., 2000). In particular, the drug can cause cardiac damage due to mitochondrial dysfunction (Zhao, 2019), apoptosis, necrosis, and oxidative stress in cardiomyocytes that is triggered by reactive oxygen species (ROS) (Qian et al., 2018). These shortcomings reduce the overall survival rate of cancer patients treated with cisplatin-based therapies when there is no available counter treatment (Tarnowski, et al., 2019).

Methotrexate (MTX)

Methotrexate an antimetabolite antifolate drug that is used to cure numerous malignant tumors i.e., choriocarcinoma, trophoblastic cancer and non-malignant disorders. (Chan and Cronstein 2013; Agarwal et al., 2010) It is the first rational drug that is mainly designed for treating acute lymphocytic leukemia. MTX is considered an effective drug to be used in chemotherapy, autoimmune disorders, tumors, osteosarcomas, and psoriasis, due to its ability to affect the levels of thymidylate, proteins, RNA, and particularly DNA by inhibiting their synthesis. (Ali et al., 2014; Gautam et al., 2016; Kalemci et al., 2015).

MTX exhibits a specific mechanism of action for its use in chemotherapy. It enters the cell via human-reduced folate carriers (SLC19A1), which leads to the formation of methotrexate polyglutamate. The transformation of dihydrofolate into tetrahydrofolate is catalyzed by the enzyme dihydrofolate reductase. Tetrahydrofolate is the active form of folic acid and is inhibited by methotrexate and methotrexate-polyglutamate (Mikhaylov et al., 2019). This disruption in nucleotide and DNA synthesis has a cytotoxic effect and therefore it is used in cancer treatment (Singh et al., 2019).

MTX has been reported to induce apoptosis as well as cytotoxic effects against various sorts of cancerous cells (Bergner et al., 2012). However, the clinical use of MTX has been restricted owing to its different side effects such as kidney damage, liver toxicity, and gastrointestinal toxicity (Ali et al., 2014). Low-dose administration of MTX does not have any side effects but chronic high-dose intake can induce several toxicities in the body. Hepatic toxicity caused by the overproduction of ROS is considered the major side effect due to the long-term medicinal use of MTX. Methotrexate hepatotoxicity due to ROS adversely affects both non-enzymatic and mitochondrial enzymatic antioxidant defense systems (Moghadam et al., 2015). It is reported that a high dose of methotrexate notably decreased the levels of GSH and NADPH that leads to escalation in hepatotoxic effects while increasing ROS. This depletion in the cellular defense system results in severe hepatic oxidative damage (Hemeida & Mohafez, 2008).

The increased ROS level and blockage of the antioxidant defense system also cause nephrotoxicity by stimulating polymorphonuclear neutrophils (Kolli et al., 2009). The excess of free radicles weakens the endogenic defense system, induces organ toxicity, and disintegration of the cell membrane (Peyrou et al., 2007). Therefore, malic acid enzymes and NADPH-dependent dehydrogenases are reduced by methotrexate, and hence NADPH production is inhibited. Glutathione reductase enzymes use NADPH to protect against oxidative stress in normal conditions. Methotrexate decreases glutathione levels by interfering with antioxidant enzyme activities (Ulusoy et al., 2016). MTX increases serum urea and creatinine levels which results in kidney damage (Abdel-Raheem & Khedr, 2014). This increase in the levels is due to cystic dilation of the tubular lumen in renal tissues accompanied by acute infiltration of inflammatory cells as well as hypertrophy and atrophy in specific glomeruli (Abdel-Raheem & Khedr, 2014).

Paclitaxel (PTX)

Paclitaxel, a dominant member of the taxane family, is considered an important chemotherapeutic agent (Zhu & Chen, 2019). Taxanes, including paclitaxel and other members of this family, are commonly used in the treatment of different cancers and primary stages of cancerous cells as well. They occur naturally and belong to the genus Taxus. Paclitaxel is derived from Taxus brevifolia. It is a tricyclic diterpenoid compound with the chemical formula C47H51NO14 (Wani et al., 1971). PTX is used to treat various kinds of diseases like ovarian cancer, melanoma, and hepatocellular carcinoma.

PTX has a distinctive action mechanism from other common tubulin-binding chemotherapeutic medicines. The other tubulin-binding chemotherapeutic drugs act by preventing tubulin from accumulating in microtubules. PTX has a mechanism of allowing tubulin accumulation in microtubules, thereby enhancing microtubule stability. This unique mechanism leads to cell cycle arrest, mitosis inhibition as well as growth suppression, and proliferation in cancer cells (Weaver, 2014).

Mitotic apparatus is a primary component formed by the microtubules entirely in eukaryotic cells (Fong et al., 2013). PTX plays a role as an anti-cancer drug by binding itself to the β -β-subunit of tubulin proteins. This binding stimulates the assembly and polymerization of tubulin, resulting in stabilizing the development of microtubules. This phenomenon disrupts the functioning of the mitotic spindle, that origins mitotic arrest on the G2/M phase and thus causes apoptosis of cancer cells (Snyder et al., 2001). Furthermore, it is observed that PTX inhibits tumor angiogenesis and triggers

the cytokines and gene expression that suppress the growth of cells and induce cell death (Taghian et al., 2005). The cytotoxic and anti-proliferative effects of PTX increase its antitumor efficacy (Fauzee et al., 2011). Potential side effects of paclitaxel include neurotoxicity, cardiotoxicity, hepatotoxicity, and so on (Cirrincione et al., 2020).

Neurotoxicity is observed in 60-70% of patients undergoing treatment with paclitaxel. This condition primarily damages somatosensory axons in soles and palms resulting in sensations of numbness, tingling, pain, and temperature sensitivity (Park et al., 2011). First, the degeneration of unmyelinated terminal arbors of somatosensory axons occurs (Bennett et al., 2011). The degeneration of the axon is initiated by the over activation of the matrix-metalloproteinase, MMP-13. MMP-13 is considered to increase epidermal matrix degeneration and may also cause axon degeneration (Cirrincione et al., 2020). However, the chances and acuteness of paclitaxel-induced peripheral neuropathy have been correlated with an increased dose and the frequency of exposure. Neuropathy is observed more in the patients receiving weekly administration than in the patients with another schedule (Sparano et al., 2008).

PTX administration can cause cardiotoxicity by elevating the serum activity of Lactate dehydrogenase (LDH) and creatine kinase-myoglobin binding (CK-MB). The heart of the paclitaxel-treated patients shows various adverse changes including lesions, presence of apoptotic and inflammatory cells, and necrosis of cardiac muscles. PTX treatment resulted in a rise in the LDH and CK-MB serum activity along with cytoplasmic vacuolation of heart muscles (Khaled et al., 2022). The rise in LDH activities in paclitaxel-treated patients is related to oxidative pre-hemolytic injury. PTX also affects adult cardiomyocytes by altering myofibrillar structure and function and induces apoptosis in cardiac tissues (Simao et al., 2006). It is also observed that PTX causes an elevation in the intensities of lipid peroxidation and Nitric Oxide in the heart. Furthermore, PTX- administration also induces renal damage by the generation of ROS and results in oxidative stress. Additionally, pathological lesions, including diffuse edema, hemorrhage, hyaline exudates, congestion, and necrosis are observed in PTX treatment (Malekinejad et al., 2016).

Tamoxifen (TAM)

In medical oncology, tamoxifen (TAM) was the first and is still regarded as one of the most revolutionary drugs. Over the past forty years, it has saved countless lives and advanced to play a major role in our healthcare system (Jordan, 2003). TAM is currently an increasingly prevalent anticancer drug that is most commonly administered globally for the chemoprevention of high-risk breast cancer (Potkul et al., 2016). Since TAM blocks estrogen receptors in breast tissues, it reduces the effects of estrogen. TAM is known as an anti-estrogen. For premenopausal women with ERα positive cancers of the breast, TAM is still the first-choice adjuvant treatment. It is also frequently administered to postmenopausal women with ERα positive tumors. TAM blocks the ERα signaling pathway in ERα+ breast cancer cells by acting as an antagonist to ERα. TAM medication greatly lowers the incidence of reappearance of contralateral breast tumor and breast cancer. Millions of individuals with ERα+ breast cancer which makes up 70% of all cases of breast cancer have been prescribed TAM since its inception in the 1970s (Jordan,1997). Due to the use of non-steroidal testosterone inhibitors in the treatment of patients with prostate cancer, TAM has been utilized as an unapproved treatment for male infertility, breast cancer, idiopathic gynecomastia, and more recently, iatrogenic gynecomastia (Hedlund, 2000; Kunath et al., 2012). Unfortunately, the emergence of tamoxifen resistance makes the efficacy unsatisfactory. It is believed that resistance to tamoxifen is closely associated with RTKs (receptor tyrosine kinases) and the activation of the PI3K-PTEN/AKT/mTOR pathway brought on by RTK overtime (Hosford & Miller, 2014).

Unfortunately, many patients suffer from tamoxifen-related adverse consequences, including hot flashes, arthralgia, dry vagina, mood swings, as well as sleeplessness, during this protracted therapy period (Land et al., 2006). A severe and dangerous side effect of postmenopausal tamoxifen medication is an increased threat of endometrial lesions, including carcinomas, sarcomas, polyps, and hyperplasia (Jones et al., 2012). Dosage reductions for people who have a lot of adverse effects may be one way to address the issue. In response to this, approximately twenty percent of patients stop taking tamoxifen during the first year of treatment, and another 5 to 10 percent of patients stop taking it completely throughout the remaining time. (Murphy et al., 1998).

Letrozole (LTZ)

Patients with postmenopausal breast cancer who are positive for estrogen receptors and who have not responded to tamoxifen or other hormonal treatments are treated with third-generation aromatase inhibitors. (Compos, 2004). Compared to aminoglutethimide, which was first marketed as the first clinically relevant aromatase inhibitor, LTZ is more selective and more tolerated (Lipton et al., 1995). However, numerous investigations have documented adverse drug reactions (ADR) and LTZ's toxicity in a number of bodily systems. (Gharia et al., 2017). Third-generation aromatase inhibitors (AI), namely LTZ, have less adverse effects, for instance musculoskeletal pain and fatigue, which affect the medication's adherence. Common musculoskeletal symptoms include stiffness in the joints, pain in the bones, discomfort in the muscles, and muscle weakness (Geisler 2011).

Hepatitis and autoimmune symptoms have been observed in postmenopausal female patients treated for breast cancer for three months with letrozole (Gharia et al., 2017). Previous research has linked these symptoms to vitamin D deficiency and decreased estrogen levels brought on by letrozole medication (Prieto-Alhambra et al., 2011). The most frequent side effects associated with the treatment were thinning hair, nausea, and hot flashes. It may be necessary to monitor LTZ's long-term influence on mineral density of bones and lipid profile, as these factors are not established yet.

5-Fluorouracil (5-FU)

5-fluorouracil (5-FU) is extensively administered to treat solid tumors like pancreatic and colorectal (CRC) cancers

(Chalabi-Dchar et al., 2021). This antimetabolite agent targets the metabolic enzymes responsible for metabolism of nucleotide or folate cycle, thus disturbing the nucleotides synthesis and one-carbon metabolism (Ser et al., 2016). 5-FU undergoes phosphorylation and generates 5-fluorouridine triphosphate (5-FUTP), 5-fluorodeoxyuridine monophosphate (5-FdUMP), and 5-fluorodeoxyuridine triphosphate (5-FdUTP) metabolites. These metabolites play a crucial role in exerting cytotoxic properties (Chalabi-Dchar et al., 2021). It hinders cell growth and induces apoptosis at the tumor site by affecting the TS (thymidylate synthase) and directly incorporating the metabolites to DNA and RNA (Wang et al., 2004). 5-FU bears resemblance with uracil (pyrimidine) by replacing the hydrogen atom with a fluorine atom at C-5 (carbon 5) and gets similarly incorporated to DNA and RNA (Blondy et al., 2020), thus modifying their metabolism (Chalabi-Dchar et al., 2021).

TS is the principal enzyme associated with 5-FU metabolism (Wang et al., 2004). If altered, it may promote 5-FU resistance; other cellular functions, such as apoptosis, autophagy, glucose metabolism, and respiration, may also be modified in relevant cells (Wang et al., 2004). TP53 is a tumor suppressor gene, and it instigates cancer cell death through apoptosis in chemotherapies and can stimulate 5-FU resistance if p53 gene is modified (Chen et al., 2017). Inhibition of the p38MAPK pathway promotes CRC cell resistance by causing a decrease in 5-FU-induced p53-driven apoptosis (Li et al., 2015). However, 5-FU chemoresistance due to continuous 5-FU treatment can be overcome by developing new drug combinations (Lee & Lee, 2019). 5-FU chemotherapy ensures disease-free survival of people diagnosed with CRC, breast, head, neck, and aero-digestive malignancy (Wang et al., 2004). Unfortunately, it is capable of affecting healthy body cells alongside killing the tumor cells; some of the rare but significant cytotoxic effects are cardiac, neurologic pathologies, hyperammonemia, or encephalopathy (Thomas et al., 2016). The cardiotoxic effects include cardiac arrhythmias, ischemia, myocarditis, heart failure, and coronary vasospasm (Faheem et al., 2022). The cytotoxicity of 5-FU on Central nervous system (CNS) stem cells are undivided oligodendrocytes, myelin pathology, and destruction of the myelinated axons in the white matter of brain and spinal cord (Han et al., 2008).

Bleomycin (BLM)

The antibiotic bleomycin (BLM) is a glycopeptide that was isolated from bacteria Streptomyces verticillus (Umezawa et al., 1966) and used to cure Hodgkin's lymphoma, squamous cell tumor, ovarian tumor, and most prominently testicular malignancy (Müller et al., 2021). It is an S- phase independent clastogen; exhibits cytotoxic effects by generating free radicals (Bolzan & Bianchi, 2018) and disintegrating the single and double-strands of DNA (Mirabelli et al., 1985; Sikic, 1986). The DNA cleavage is site-specific as the maximum cleaved dinucleotide DNA sequence is 5′-GT*, whereas the site least susceptible to cleavage is with a 5′-GC* dinucleotide sequence. Interestingly, the alternate purine-pyrimidine base pairs are highly prone to cleavage by bleomycin (Murray et al., 2016). DNA damage repair is the primary mechanism for drug resistance against chemotherapeutic drugs (Murray et al., 2014). An effective BLM resistance includes a decline in cell cycle arrest at G2/M stage, damage DNA and decreased apoptosis (Wang et al., 2013).

There are various BLM-induced side effects reported in cancer patients; the most severe is pulmonary toxicity (Raphael et al., 2020), which impairs lung function and causes pulmonary fibrosis (Müller et al., 2021) and it may lead to the demise of patients. These side effects restrict its role as a chemotherapeutic agent. The single dose of BLM is capable of inducing sub-chronic effects but severe, long-lasting effects upon repeated administration of the drug (Latta et al., 2015). BLM causes severe pneumonitis. The main reason for developing pneumonitis is the production of cytokines and free radicles and subsequent endothelial damage of the vascular system of the lung (Uzel et al., 2005). Interstitial pneumonitis is the most common BPT (bleomycin pulmonary toxicity), and it can develop into pulmonary fibrosis. Other forms of BLM-induced pulmonary toxicity include eosinophilic hypersensitivity and bronchiolitis obliterans organizing pneumonia (Shippee et al., 2015).

Another adverse influence of BLM therapy in patients of testicular cancer is flagellate dermatitis; some of the collective histological modifications are spongiotic dermatitis, dermal edema, lymphocytic infiltrate with neutrophil and eosinophilic granulocytes, and epidermal hyperpigmentation (Ziemer et al., 2011). The toxic effects of BLM are abolished by the genes encoding the BLM hydrolase enzyme (Müller et al., 2021). Since bleomycin hydrolase (BLMH), a bleomycin-inactivating enzyme (Jona et al., 2016), constitutes very deficient levels or is absent in lungs and skin, that justify the manifestation of BLM toxicity in these organs (Shippee et al., 2015).

Vincristine (VCT)

Vincristine (VCT) is found in Madagascar periwinkle (Catharanthus roseus; Apocynaceae). It was initially isolated and characterized by Svoboda et al. in 1961 (Neuss et al., 1962). VCT is the most common vinca alkaloid and is widely used in chemotherapy regiments to treat pediatric acute lymphoblastic leukemia (ALL) and various other malignancies, including sarcomas, lymphomas, neuroblastoma, renal tumors, liver tumors, breast and brain cancer. VCT's action mechanism is associated with cell division arrest in metaphase through binding with the β-subunit of tubulin (Dumontet & Jordan, 2010). Tubulin dimers consist of α- and β-subunits of tubulin protein, where the β-subunit acts as a binding site for vincristine (Field et al., 2014). Due to its mechanism of action, it is regarded as a mitotic poison (Skubnik et al., 2021).

During VCT therapy, its antimitotic effect is not only limited to cancer cells, but thereby alters the cell division in intestinal mucosa that may induce nausea, vomiting, or diarrhea (Boussios et al., 2012). However, it has dose-limiting neurotoxicity, causing severe motor and sensory damage in vincristine-induced peripheral neuropathy (VIPN) (Smith et al., 2015; Verma et al., 2020). It is demonstrated by numbness, tingling, and bilateral pain in limbs or muscle weakness, thus,

negatively affecting the life quality of patients (Verma et al., 2020). After vincristine treatment children were less responsive to touch, pinprick sensation, and temperature differences when hot or cold objects were applied to their skin.

Other neuropathies may involve damage to cranial nerves, hyporeflexia, and autonomic neuropathy. Indicators of involuntary neuropathy include orthostatic hypotension, urinary retention, and constipation (Argyriou et al., 2006; Gomber et al., 2010). Though, the said side effects can be avoided by reducing the doses of vincristine by (Skubnik et al., 2021) by applying combination therapy (Table 2).

CONCLUSION

Cancer is a complex ailment that results from epigenetic or genetic changes while chemotherapy plays a vital role in treating cancer with significant drawbacks as it instigates potential toxicities to organs. The drugs like doxorubicin, cisplatin, methotrexate, paclitaxel, tamoxifen, letrozole, 5-flurouracil, vincristine and bleomycin though effective against cancer, can also cause damage to the heart, liver, kidneys, and nervous system. As global cancer cases are expected to rise so it is crucial to not only focus on treating cancer but also on lessening the negative impact of these treatments. Future research needs to strike a balance between fighting cancer and safeguarding the overall health of patients. Advancing towards treatments that are less toxic and more sophisticated, along with approaches specified to patient needs, is essential. As our knowledge of the mechanisms of cancer grows and our range of treatments broadens, our goal is not just to prolong the lives of cancer patients but also to improve their life quality by reducing the unintentional harm caused to their vital organs by different drugs.

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Table 2. Different chemotherapeutic drugs, their action and adverse impacts

Drugs	Treatment	Side effects	Citations
Doxorubicin	Widely used against breast, uterine, ovarian, lung and cervical cancer.	Major obstacles are doxorubicin-induced cardiotoxicity as well as the mechanisms of cancer drug resistance.	Al-Malky et al., 2020; Vyas et al., 2020
Cisplatin	Primarily used to treat ovarian cancer, although it is also used to treat lung, testicular, and bladder malignancies.	Intoxication to the most vital organs, including the inner ear, liver, heart, and kidneys. As well as modifications to the systems that repair DNA damage and various alterations to the apoptotic and autophagic processes.	Zon & Bednarek, 2023
Methotrexate	Used to treat several malignant conditions, including uterine, breast, and lung cancer.	While MTX side effects and toxicity, including bone marrow suppression, lung toxicity, nephrotoxicity, hematologic toxicity, and an elevated risk of infections, can occur with higher dosages.	Hamed et al., 2022
Paclitaxel	Utilized to treat malignancies of the breast, colon, esophagus, lung, cervix, and prostate	Hair loss, allergic reactions, vomiting and nausea, bone marrow suppression, neutropenia, leukopenia, anemia, arthralgia, myalgia, mucositis, and neuropathy are among the common side effects of paclitaxel.	Asnaashari, et al., 2023
Tamoxifen	Widely used to treat and prevent breast cancer, it is regarded as a groundbreaking medication.	Tamoxifen medicine for postmenopausal patients has several significant and dangerous side effects, one of which is a higher risk of endometrial lesions, including hyperplasia, carcinomas, polyps and sarcomas.	Jones *et al*; 2012; Ahmad, 2018
Letrozole	Operative in treating postmenopausal women with hormone-sensitive breast cancer.	Musculoskeletal pain and fatigue. Hepatitis and autoimmune symptoms have also been seen.	Murphy, 1998; Gharia et al; 2017
5-Fluorouracil	Frequently used to treat various malignant tumors, such as malignancies of the breast, pancreas, skin, stomach, esophagus, and head and neck.	Restricted because of medication resistance. Other issues include ineffectiveness and systemic toxicity.	Vodenkova et al., 2020
Vincristine	Treat lymphomas, neuroblastoma, sarcomas, and central nervous system tumors.	A serious and dose-limiting adverse effect of vincristine is neurotoxicity, also can cause symmetric and peripheral nerve damage.	Mora et al., 2016
Bleomycin	Treat lymphoma and germ cell tumors.	Pneumonitis and pulmonary fibrosis are the two most dangerous side effects of bleomycin and some other lung pathologies include organizing pneumonia and eosinophilic hypersensitivity pneumonitis.	Groselj et al., 2016

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