A prospective study on adverse events and medication errors associated with chemotherapeutic treatment at an inpatient department in a tertiary care hospital

[1]SHARON SUSAN RAJ, [2]Dr. SHIBI MARY THOMAS, [3]Dr. BLESSY K GEORGE

[1]Pharm.D intern; [2]M. Pharm, PhD; [3] Pharm.D
[1]Department of Pharm.D
[1]Karnataka College of Pharmacy – 560064, Bengaluru, Karnataka, India. 7619311958.

Abstract

Background: Morbidity due to medical errors is one of the leading risks to the world's health. In the context of an unstable environment as well as hereditary evolution, tumors become a constant threat in everyday life. Chemotherapeutic agents discovered as a hope in the journey against tumors often come with associated side effects. Taking our view through the pattern of side effects seen along with the most commonly prescribed chemotherapeutic agents and the type of errors that occur at an oncology setup in the hospital would help the clinicians and other health care workers to have better knowledge and patient safety.
Objectives: Assessment of side effects with commonly prescribed chemotherapeutic agents was the primary objective, whereas the medication safety associated with the latter was taken as the secondary objective.
Method: It was a prospective observational cross-sectional study in which 134 patients' prescriptions were analyzed to assess the chemotherapeutic side effects as well as the medication errors while handling the chemotherapeutic agents in a hospital setup.
Results: The study was conducted on 134 patients and there were around 27 types of tumors that were treated. Around 80% of the population belongs to the age group of 20 - 65 years and breast cancer is the top most treated tumor, 68.6% of the sample population was women.
There were 10 classes of chemotherapeutic agents used and Cisplatin stands as the highest used drug. Upon checking the side effects, nausea, vomiting, and diarrhea were seen in the majority of the sample population. On the other hand, there were 34 prescriptions and 16 administration errors seen during the treatment period.
Conclusion:
The study on adverse effects of chemotherapeutic agents has been studied along with the type of prescription and administration errors that occur during the treatment. The study saw various side effects that the patient undergoes in the course of the treatment. It also shows a torch towards the possibility of different types of medication errors that can lead to worse outcomes or increased hospital stay and financial burden to the patients. This study becomes highly significant when seen in the context of a developing country.

Keywords: medication safety, chemotherapeutic drugs, adverse effects, error in prescription, administration errors

Introduction

Drug utilization research was defined by WHO in 1977 as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences. The rational use of drugs in the population was the primary aim of drug utilization research. By coining the term, "rational use of drugs", the importance of a well-documented prescription at the right dose for an affordable price with the right information to the patient is significantly evident. Lack of knowledge of the prescription pattern can be a decelerating force on discussion and improvement in the prescription habits. (1). Proper evaluation of the prescription pattern at regular intervals leaves the physician with an extremely useful quality assurance option by updating the prescription with the most recent trends as well as getting the prescriber feedback from across the landscape. According to different reports provided by various authorized researchers across the globe, adverse drug reaction-induced hospitalization was found to be less than 10 % of the total hospitalized cases. (2), (3). In a developing country like India, where 21.9% of the population is still under the poverty line, the amount of burden induced on them is not hidden. (4). Critical evaluation of the prescription by the physicians could therefore help in the overall quality of the patient's life.
Times of India, based on 2010 to 2012 data, reported the most invasive killer's prevalence with an estimated 14.5 lakh people living with Cancer on our mainland. (5)
WHO's report tells us more about the relevance of updating on this issue when they predict that 19 million people would defend themselves in the war field against cancer. (6) Treatment modalities of cancer range from localized therapy which include radiation as well as surgery to systemic treatment which provides treatment through chemotherapy, targeted therapy, immunotherapy, and so on. (7) Cancer is a collection of the disease known for its invasiveness and metastasis. Depending upon its benign or metastatic nature, invasiveness and metastasis are present either alone or together respectively. (6) The main aim of chemotherapy is to shrink the cells before radiation or surgery as well as to clean out the cells after the main treatment. (8) Appropriate use of chemotherapy helps in destroying highly proliferative cells as well as in preventing or extending the period between the relapse.

Despite the hope provided by the chemotherapeutic agents, there is always a gravitational force holding back from its utmost potential as side effects. Since the chemotherapeutic agents mainly focus on rapidly proliferating cells, the drugs more often tend not to differentiate between normal cells undergoing proliferation to cancer cells that are rapidly dividing. This phenomenon of acting against all rapidly proliferating cells leads to side effects. (9) Having a perspective on the pattern of side effects would help physicians across the globe to come into more individualized therapy for a different specific population. The review of this kind of report would guide the physicians in making modifications while changing the dosage amounts, intervals, route of administration, etc. (10)

Getting onto a closer version of drug utilization, human possible errors are also possible. This, in turn, contributes to the added effect of irrational drug use resulting in adverse drug reactions, the economic burden to the patients, and higher complications upon the already existing pathological conditions. Evaluating the pattern of errors could necessarily outline the sectors which needed to be carefully approached to minimize the possibility of error occurrence. The above initiative can accessorize the physician in providing better patient care and overall a better society indeed.

Methodology

The main aim of the study was to assess the prescription pattern of chemotherapeutic drugs and the side effects associated with them. Along with that, the levels of errors occurring at the prescription and administration levels were also calculated. The study protocol was approved by the institutional board and the ethical committee. Patients who fall by the inclusion criteria were reviewed for the study purpose.

The study was a prospective observational cross-sectional study, where the prescription pattern of chemotherapeutic agents along with the types of adverse reactions seen in patients undergoing chemotherapy was evaluated. On the other hand, the inpatient medication charts were reviewed for observed prescription and administration errors. The study completed its 11 months in a tertiary care hospital under the supervision of the appointed oncologist. The study data went through a vigorous evaluation of the demographic details of patients and types of malignancy seen in both genders and also the different types of adverse reactions seen in different organ systems of the patients taking chemotherapeutic agents. The data was later conceived to get a clearer version of the study.

Result

The patients taking chemotherapeutic agents were initially classified based on 3 age groups more than 4/5th of the population fall in the category of 20 to 65 years while 1/10th of the population fall above the 65 years old age category and less than 1/10th belongs to less than 26 years old age group. Almost 27 types of malignancies were observed during the study. In that, 20 types of tumors were observed in females and 15 were observed in males. Breast cancer was the most predominant in females as 34 of them were diagnosed with breast cancer and blood and bone marrow malignancy tops in males as 6 out of 42 male patients reported sharing the above variety of malignancy. Upon treatment with chemotherapeutic agents, 10 chemotherapeutic classes of drugs were used and the platinum coordination complex class of drug was highly used with cisplatin being prescribed for 29 patients out of 134 patients studied.

On observation of adverse drug reactions, the GI system was highly affected as vomiting, nausea and diarrhea were the highly reported side effects and the least noted side effects include sweating, hot flashes, and pain. The study results also peep through the type of errors that can be made during the provision of treatment to the patients, which include both prescription and administration errors. Out of the total 50 errors obtained 34 were marked to be prescription errors and drug interactions stand as the highest number of errors seen having a count of 14.

Table 1

The demographic details of the study population along with the types of tumors observed based on gender has been given as follows:

Demographic details of the patient			
Demographic details	**Parameter**	**No. of samples (134)**	**Percentage (%)**
Age (Years)	0 - 26	10	7.462
	20 - 65	110	82.089
	>65	14	10.44
Gender	Male	42	31.343
	Female	92	68.656
Types of tumors observed in sample population			

Types of tumors	No. of females (92)	Percentage of females (%)	No. of males (42)	Percentage of males (%)
Breast	34	25.373	0	0
Ovarian	4	2.985	0	0
Lung	4	2.985	4	2.985
Lupus	2	1.492	0	0
Thyroid	0	0	2	1.492
Brain	2	1.492	0	0
Skin	0	0	2	1.492
Non-Hodgkin Lymphoma	4	2.985	4	2.985
Skin and muscle	2	1.492	0	0
Neck	2	1.492	0	0
Colon	4	2.985	4	2.985
Blood and bone marrow	8	5.97	6	4.477
Soft tissue	2	1.492	2	1.492
Stomach	4	2.985	0	0
Anorectal	0	0	2	1.492
Uterus	2	1.492	0	0
Bone	2	1.492	0	0
Oral	2	1.492	4	2.985
Tongue	0	0	2	1.49
Peritoneal	2	1.492	0	0
Head and neck	2	1.492	2	1.492

Rectal	0	0	2	1.492
Testicular	0	0	2	1.492
Tonsil	2	1.492	2	1.49
Cervical	4	2.985	0	0
Oesophageal	4	2.985	0	0
Larynx	0	0	2	1.492

Table 2
The prescription pattern of chemotherapeutic agents used by the sample population is as follows:

A. The pattern of chemotherapeutic agents			
Name of chemotherapeutic drug	**Class of drug**	**No. of prescriptions having each drug**	**Percentage (%)**
Cisplatin	Platinum based chemotherapeutic drug	29	21.641
Carboplatin	Platinum based chemotherapeutic drug	23	17.164
Paclitaxel	Taxane(Microtubule inhibitors)	19	14.179
Oxaliplatin	Platinum based chemotherapeutic drug	17	12.686
Docetaxel	Taxane (Microtubule inhibitors)	15	11.194
Doxorubicin	Antitumour antibiotics (Anthracyclines)	15	11.194
Cyclophosphamide	Alkylating agents	13	9.701
Vincristine	Microtubule inhibitors(Vinca alkaloids)	9	6.716
Etoposide	Topoisomerase inhibitors	7	5.223
Zoledronic acid	Bisphosphonate (Combinational drug)	5	3.731
Methotrexate	Antimetabolites	5	3.731
Fluorouracil	Antimetabolites	5	3.731
Ifosfamide	Alkylating agents	5	3.731

Leucovorin	Folic acid analogue (Combinational drug)	5	3.731
Bendamustine	Alkylating agents	3	2.238
Atgam	Folic acid analogue (Combinational drug)	3	2.238
Daunorubicin	Antitumor antibiotics (anthracyclines)	3	2.238
Vinorelbine	Vinca alkaloids (Microtubule inhibitors)	3	2.238
Rituximab	Monoclonal antibodies	3	2.238
Epirubicin	Antitumour antibiotics (Anthracyclines)	3	2.238
Pemetrexed	Antimetabolite	3	2.238
Anastrozole	Nonsteroidal aromatase inhibitors	1	0.746
Irinotecan	Topoisomerase inhibitors	1	0.746
Gemcitabine	Antimetabolite	1	0.746
Bleomycin	Antitumor antibiotics	1	0.746
Bortezomib	Antineoplastics, proteasome inhibitors	1	0.746
Trastuzumab	Monoclonal antibiotics	1	0.746

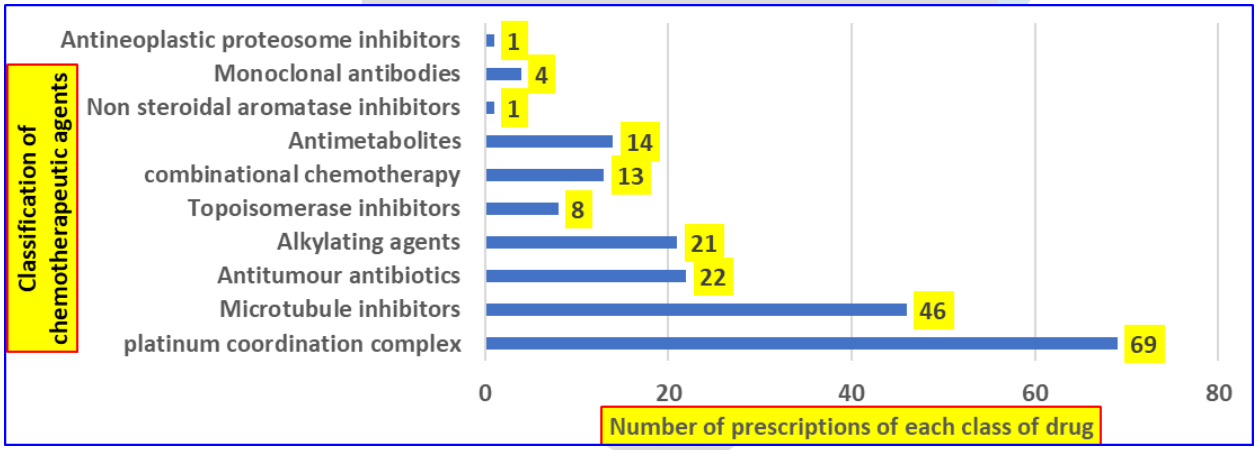

Figure 1
Number of prescriptions of each class of chemotherapeutic drugs

Table 3
Distribution of side effects based on organ system

Organ system	**Side effects**	**Number of individuals with mentioned side effects**	**Percentage (%)**
GIT	Vomiting	126	94.029

	Nausea	120	89.552
	Diarrhea	101	75.373
	Decreased appetite	62	46.268
	Abdominal pain	33	24.626
	Constipation	33	24.626
Heme and Lymphatic	Bleeding	39	29.104
	Risk of infection	31	23.134
	Anemia	27	20.149
	Leucopenia	10	7.462
	Thrombocytopenia	8	5.97
	Bone marrow suppression	6	4.477
	Hemolysis	4	2.985
Musculoskeletal and Connective tissue	Joint Pain	33	24.626
	Muscle Pain	18	13.432
Renal and Urinary disorders	Blood in urine	14	10.447
	Bladder irritation	4	2.985
Skin and subcutaneous tissue disorders	Alopecia	49	36.567
	Bruising	35	26.119
	Nail discoloration	29	21.641
	Change in skin color	6	4.477
	Sweating	2	1.492
Nervous System	Neuropathy	29	21.641
	Dizziness	4	2.985
	Headache	4	2.985
	Insomnia	4	2.985
Allergic reactions	Swelling	10	7.462
	Anaphylaxis	8	5.97
	Redness	8	5.97
	Rashes	6	4.477
	Itching	4	2.985

	Serum sickness like syndrome	4	2.985
	Hot flashes	2	1.492
Metabolism and nutritional disorders	Loss of taste	23	17.164
	Anorexia	4	2.985
Infections	Sore mouth	29	21.641
	Fever	14	10.447
	Chills	12	8.995
	Non healing wound	6	4.477
	Sore eye	2	1.492
	Anal Ulceration	2	1.492
Other general reactions	Pain	85	63.432
	Weakness	37	27.611
	Hypotension	31	23.134
	Respiratory distress	8	5.97
	Missed menstrual period	6	4.477
	Fatigue	4	2.985
	Hepatic dysfunction	4	2.985
	Chest Pain	2	1.492

Table 4
Types of medication errors

A. Prescription Errors		
Types of prescription error	Number of prescription errors	Percentage of prescription errors (%)
Drug interactions observed	14	41.176
Incomplete order	4	11.764
Poorly written medication order	4	11.764
Not mentioned patient's age	4	11.764
Date of prescription not mentioned	2	5.882
Illegible handwriting	4	11.764
Misinterpreted handwritten prescription error	2	5.882
Total	**34**	**100**

B. Administration Errors		
Types of administration errors	Number of administration errors	Percentage of administration errors
Wrong dose administration	4	25
Breached established guidelines	4	25
Error in the rate of administration	2	12.5
Failed to give medication	2	12.5
Wrong administration technique	2	12.5
Missed dose administration	2	12.5
Total	**16**	**100**

Discussion

The study opens an insight into the hour's emergency to be updated about the emerging and changing strategies against the widely fledged silent killer, Cancer. Regular feedback through research offers better strategies and overall improvement in patient care. The review of prescription patterns accessorizes the physician in making better decisions based on the geographical alterations seen in the genetics of different populations. 4/5th of the population falls into the age range of 20 to 65 and it has to be further noted that female cancer patients account for 68.7 percent of the total population. The discrepancies in the majority of the sample falling into the 20 to 65 age group could be explained by the range of ages this group is covering as compared to the 0 to 20 and more than 65 age group. The study offered by NIH is convinced of the fact that DNA methylation increases with age and increased methylation could alter the genes responsible for controlling cell development and favor the cell being transformed into a cancer cell, which is why the percentage of cancer is higher in old age than in the younger generation. (11) According to the WHO report of 2020, breast cancer incidence was the highest of the year among all the other types of cancers, and having a greater proportion of the sample falling into breast cancer could explain the sample having higher female candidates in the study. (12)

Under the drugs used, platinum coordination complex and microtubule inhibitors were the major class of drugs used. Cisplatin and carboplatin being the highly prescribed drug could answer the platinum coordination complex being the major class of prescribed drugs. Having a major group of the sample population diagnosed with ovarian cancer, lung cancer, head, and neck cancer, and testicular cancer tells us about carboplatin and cisplatin being majorly prescribed. (13) By using the platinum coordination complex, the replication of RNA is prevented and that causes the breakage of DNA strands and miscoding, which eventually manifest as apoptosis or RNA/protein synthesis inhibition. (14). Talking about microtubule inhibitors, docetaxel and paclitaxel are indicated for lung cancer, ovarian cancer, and breast cancer. (13) And the proportion of people with the latter mentioned cancers is very high. Considering the scenario, one could be verified of these drugs take up the larger part of the prescription. These agents accelerate the marshaling of microtubules and block them from depolymerization. (15) Once depolymerization is prevented, microtubule function in mitosis is restricted, constricting the cell from undergoing division and resulting in the failure of apoptosis. (16) Other major classes of drugs used were antitumor antibiotics and alkylating agents. Antitumor antibiotics target cancer cells and prevent them from proliferating by acting at their genetic level. Here the major class of antibiotics used were anthracyclines and bleomycin. Anthracyclines interact with DNA and the enzymes which work together with it. DNA needs to be copied before cell division is inhibited. This causes the cell to put a pause on its multiplication ability, whereas in the case of bleomycin, it produces free radicals which cause DNA damage in cancer cells. (17) . Noting down the action of alkylating agents, it is exemplary that they work during all the phases of the cell cycle. It cross-links N7 guanine residues leading to abnormal pairing that in turn causes the DNA strands to break up, which is further followed by cell death.

Going by Indian mythology, even the elixir of life has its side effects, if taken in excess. But the current medicinal scenario is still struggling with the anticipated and unanticipated side effects observed with its treatment options and chemotherapeutic drugs would be at the peak zone, considering the above fact. The side effect profile of the drugs used during the research process would outline the cautious parameters, which need to be considered while writing a prescription. Nausea is an undesired sensation in the back of the throat or epigastrium, whereas vomiting is regarded as the throw-up of contents from GIT. (18) The two apparent mechanisms explained for the displayed nausea and vomiting lie in the hands of the central nervous system and peripheral nervous system. Acute emesis which occurs within 24 hours of chemotherapeutic treatment happens by the peripheral pathway inputs received by the vomiting center of the brain placed in the medulla oblongata. Here, chemotherapeutic agents-induced stimuli like incitation on the pharynx as well as distension of the gastric/ duodenal region are taken up by the abdominal vagal afferent nervous system. The immoderate activation of afferent vagus fibers causes the overexpression of receptors such as cholecystokinin-1, neurokinin-1, and serotonin receptors, and these receptors also work along to stir up the emetic response. These fibers run to the dorsal vagal complex which has the chemoreceptor trigger zone (area prostema), nucleus tractus solitarius, and the dorsal motor nucleus as well. The nucleus tractus solitarius and up to a certain extent, area chemoreceptor trigger zone together delivers information to the vomiting center, which is further manifested as acute emesis. In the case of central emesis induced by chemotherapy, the chemotherapeutic trigger zone sends inputs to the vomiting center located on the floor of the fourth ventricle. It becomes easy for the drugs to stimulate

the receptors in the chemotherapeutic trigger zone (area prostema) as there is no blood-brain barrier around. (19) Diarrhea being reported as the second major side effect can be understood by the mechanical and biochemical alterations caused by the chemotherapeutic drugs on the bowel mucosa. (20)
Because a greater proportion of people reported reduced appetite and pain, delineating the reasons would be helpful. Since chemotherapy causes nausea and vomiting, the patients could get exhausted which results in fatigue. This along with depression and altered mood could reduce the patient's interest in consuming food. Moreover, patients could develop ulcerations in the mouth which lead to difficulty in chewing and swallowing, which could essentially interfere with appetite. (21) Pain, in turn, was reported comparatively by a greater number of the population, which could be described as nociceptive pain or neuropathic pain. Nociceptive pain happens as a result of tissue damage or by the stimulation of nociceptors (specialized peripheral sensory receptors) by chemotherapeutic agents. While nociceptive pain is short-lived, neuropathic pain is chronic and is caused by injury to the nerves directly. This is often felt as a burning, shooting, or tingling sensation and happens due to the hypersensitization of nerves. In neuropathic pain also, since the blood-brain barrier is not around the peripheral nervous system, direct toxic effects on the peripheral nervous system as peripheral neuropathy are often felt. (22) It is profoundly seen as functional inadequacy of the sensory, motor, and autonomic nervous systems. This could further go in explaining most of the side effects observed such as hypotension, constipation, altered urinary function, joint pain, muscle pain, etc. And these symptoms when clubbed occurred in higher proportion as compared to the other side effects, this is due to higher prescription usage of platinum-based drugs, and taxanes in the sample population. (23) The peripheral neuropathy due to platinum-based compounds, primarily on the sensory neurons, can be explained by the apoptosis of dorsal root ganglion, which in turn is caused by mitochondrial dysfunction, oxidative stress, DNA adducts, and crosslinks formation. (24)

Side effects involving the heme and lymphatic system were also reported in a significant number of sample populations. Chemotherapy-induced anemia is often precipitated by Platinum-based therapy and the prescription pattern used by our sample population has platinum-containing compounds as the highest prescribed drugs. The direct suppression of erythroid progenitor cells within the bone marrow as well as the toxic effects caused to the kidney by the erythropoietin-producing cells lead to the exaggeration of anemia induced by the chemotherapeutic agents. (25). Going down the lane, hematopoietic progenitor cells get recruited in case of hematopoietic stresses like major infection and bleeding as well as in chemotherapy-induced myelotoxicity. Nevertheless, since chemotherapeutic agents show higher specificity to rapidly dividing cells and do not differentiate between hematopoietic stem cells and tumors, it often displays leucopenia. Leucopenia in turn can lead to severe infections as well as anemia. (26) Thrombocytopenia which was also seen in a significant number of patients treated with chemotherapeutic agents, could be ascribed to low platelet production or higher platelet destruction. Here, in this scenario, chemotherapy-induced thrombocytopenia is more evident due to decreased platelet production than platelet destruction. Different chemotherapeutic classes exhibit action on megakaryocytes at different stages of their development. Some show anti-mitotic action on stem cells whereas others show anti-mitotic action on progenitor cells. Often, depending upon the stage of anti-mitotic action, one could predict the duration of thrombocytopenia and the refractory period to treatment. Apart from the above-mentioned way of lowering platelet production, some drugs obstruct the stimulation of nuclear factor B (NF- B), which in turn alter the capability of mature megakaryocytes to shed platelets, leading to thrombocytopenia again. (27) Thrombocytopenia could favorably explain the number of patients complaining of bruising since lack of platelets contributes towards bleeding and bruising more than the regular population.

Sometimes, hemorrhagic cystitis is seen associated with cyclophosphamide, ifosfamide, and doxorubicin, and a good number of patients were prescribed the above. Chemotherapy-induced hemorrhagic cystitis happens when acrolein (a by-product of the medication) irritates the bladder lining giving enough good reason for ulceration and bleeding. (28) Chemotherapy is known for its action against rapidly dividing tumor cells but the lack of differentiation of tumor cells from other rapidly dividing healthy cells like hair cells causes alopecia. (29) Similar to its adverse action on hair cells, it acts on rapidly dividing nail cells as well, and depending upon the component of the nail unit, the clinical manifestation of the nails are present differently. According to the American Cancer society, nail discoloration seen as hyperpigmented nails can happen with the use of Bleomycin, Cyclophosphamide, Daunorubicin, Doxorubicin, and Methotrexate. Those discolorations seen as hemorrhages (splinter hemorrhage) could happen due to Doxorubicin and Docetaxel, Paclitaxel whereas ridges, lines, creases, or other nail discoloration can occur with the potential use of Cyclophosphamide, Doxorubicin, Docetaxel, Ifosfamide and 5- Fluorouracil. (30) Hyperpigmentation seen as brown or black often tells us about Melanonychia, whereas, due to certain drug intake nails change the color to red, brown, or orange and indicate subungual hemorrhage. The horizontal lines seen as depression with partial or complete nail involvement are called beau's lines. The exact mechanism by which chemotherapeutic agents cause cosmetic nail pathological conditions isn't clear but various hypotheses have been put forward by eminent researchers. One such research study even thought of paclitaxel drug vehicles such as Cremaphor EL or Tween 80 to cause nail changes, which was reassured when the incidence of nail changes decreased while using albumin-bound Paclitaxel. Apart from this, the most valid theory of cosmetic nail differences would be because of the denervation of neuro fibers. (31)
Some drugs that inhibit the epidermal growth factor receptor alter the signaling pathways, thus inhibiting keratinocyte growth, cell death, and spontaneous lowering of cell recruitment. All this together causes keratinocytes to release cytokines which initiates a spark of inflammatory reactions leading to acneiform eruptions or vigorously itching papulopustular rashes in the seborrheic areas such as the face, scalp, and chest. Here, some of the epidermal growth factor receptor inhibitors used were Cisplatin, Carboplatin, Paclitaxel, Oxaliplatin, Doxorubicin, Vincristine, Etoposide, Daunorubicin, and Cyclophosphamide.
Sometimes, skin changes can occur when vascular endothelial growth factor receptors and platelet-derived growth factor receptors are inhibited together. This affects the repair process of capillaries and fibroblasts. Along with this profound damage, any occurrence of subclinical trauma with friction to exposed areas of palms and soles causes inflammation. This is often manifested as erythema

over the thenar, hypothenar, and pad of distal phalanges. In extreme scenarios, blisters occur in the erythematous region. The drugs which are used in our study and can cause this include Doxorubicin and 5-Fluorouracil.

Anticancer drugs are also infamous for causing hyperpigmentation. Though the underlying mechanisms have to be still unwired, several hypotheses have been set about it. Two of the main postulations are about the accumulation of drugs beneath the skin and toxicity caused by melanocytes to stimulate melanin production. It has also been said to happen due to the steep increase in adrenocorticotropic hormone and melanocyte-stimulating hormone. The drugs which usually cause hyperpigmentation and are used in our study include Cisplatin, Paclitaxel, Cyclophosphamide, Doxorubicin, Etoposide, Fluorouracil, and Bleomycin.

Paclitaxel and Carboplatin which are allegedly reported to cause burning sensation, redness, and tenderness have been prescribed to our study population as well. (32)

Chemotherapeutic agents such as Bleomycin and 5 - Fluorouracil, which are used in our study and chemotherapeutic agents as a whole are capable of causing serum sickness-like syndrome, headache, sore mouth, respiratory distress, chest pain, loss of taste, etc. This is because cancer and chemotherapy primarily affect rapidly dividing cells and more commonly, the bone marrow. Bone marrow is responsible for producing white blood cells and chemotherapy in turn weakens the immune system. This makes the patient more susceptible to more infections, thus causing all the above-mentioned fever-associated symptoms. (33)

Though neurons do not fall into the classification of fast-dividing cells, anticancer drugs still act on them and cause neurotoxicity. The mechanism by which they do this can range from direct acting upon the neuronal cell body and the neurites to indirectly causing glial damage and inflammation. The neurotoxicity affecting the brain can result in headaches, dementia, problems with consciousness, and cognitive disorders termed chemobrain. In the early 2000s, chemobrain or chemofog was called for chemotherapy-induced cognitive impairment. Chemofog is often correlated to impaired cognitive and executive functions as well as insomnia and a whole decline in health. The patient may complain that he feels dizzy because of the chemotherapeutic agents directed toward the brain and spinal cord. (34) Chemofog is postulated to be the result of neuronal injury and abnormal brain remodeling. This can be due to inflammation or abnormal endocrinological responses toward the neurons. Alongside, there is an increased inflow of cytotoxic agents and proinflammatory cytokines to neurons, astrocytes, and microglial cells due to changes in the blood-brain barrier. All this leads to chemofog in a nutshell. (35)

The reasons for sweating have to be seen from different angles. Chemotherapeutic agents can increase the susceptibility of the person to infection. Infections lead to hyperthermia and the body tries to counter-regulate the temperature by sweating. Sometimes neuroendocrinological toxicity can alter hormone levels and patients develop hot flushes and sweats. (36)

Chemotherapeutic agents can also cause dehydration due to nausea and vomiting or excessive sweating. This can make the patient have a sudden drop in blood pressure leaving the patient dizzy. (34)

Apart from other mentioned side effects of chemotherapeutic agents, they prevent angiogenesis. They impede cell migration to the wound and decrease extracellular matrix production. Collagen synthesis is decreased due to the suppression of fibroblast proliferation. In addition, the lowered immunity further decelerates wound healing. Cyclophosphamide and Cisplatin by hindering the cell cycle increase the wound healing period. (35)

Doxorubicin induces cytotoxicity of fibroblasts, thrombocytes, monocytes, and leucocytes. It also has effects on the myelosuppression of platelets and inflammatory cells. It also produces a cytotoxic effect by blocking the cell dividing capability of keratinocytes and decreasing collagen production. Doxorubicin is also infamous for associated conjunctivitis or sore eye, which gets resolved quickly on its own. Thereby, the use of this drug has a potential warning of nonhealing wounds and conjunctivitis (35)

When the intestinal mucosa gets exposed to cytotoxic agents, it results in cellular DNA damage and apoptosis by generating oxidative stress and reactive oxygen species. The reactive oxygen species induce a cascade of inflammatory pathways. This further upregulates the inflammatory mediators, which also include the nuclear factor kappa-B. Nuclear factor kappa-B, once activated by chemotherapeutic drugs and reactive oxygen species., induces the production of proinflammatory cytokines such as tumor necrosis factor, Interleukin 1β, and interleukin-6 causing tissue injury and apoptosis. It also upregulates the expression of adhesion molecules and cyclooxygenase 2 with subsequent angiogenesis. Through a positive feedback mechanism, proinflammatory mediators exaggerate the inflammatory pathway recruiting more inflammatory mediators. Altogether this causes ulceration, which is seen as anal ulceration in some patients. (37)

Since most of the chemotherapeutic drugs are metabolized through the liver, there are higher chances of toxicity to the liver and they are termed hepatotoxins. Some drugs to be used with caution include methotrexate, dactinomycin, ifosfamide, gemcitabine, etoposide, 6-mercaptopurine, and cyclophosphamide. Clinicians need to be extra careful with the drugs if the patient is already having pre-existing liver disease and those categories of drugs, which are used in our study include Anthracyclines, Taxanes, Vinca alkaloids, and Imatinib. (38)

Chemotherapeutic agents affect the female reproductive system from various sides. It can affect the hypothalamic-pituitary axis, which controls the hormonal system. In addition, oocytes (cells of the ovaries) which are responsible for the production of estrogen (a hormone that helps release eggs every month and prepare the uterus for pregnancy) are fastly dividing cells and chemotherapeutic agents tend to attack these cells, and affect fertility. (39)

Medication errors related events are one of the major preventable etiologies of morbidity and mortality. For chemotherapeutic agents as seen under the category of narrow therapeutic regimen, it is crucial to monitor the medication errors present. Overdose can lead to hazardous health outcomes for the patients and underdose can cause subtherapeutic outcomes.

Monitoring of Medication errors frequently helps the healthcare society to keep the pace in which medication events are looked at with different updated technology, the procedures used, and the type of errors that can happen in a hospital setup.

Evaluation of declared MEs, made the health care system check carefully the quality with which MEs are looked for, the procedure used, and the importance of precising the errors. (40)

Our study focuses on the most preventable side of outcome occurrence after a medication error event. This includes prescription errors and administration errors. An interdisciplinary approach among healthcare workers can reduce the type of administration errors. Often preparation of doses to administer to patients at the bedside by the nurses puts them in trouble and at higher risk of medication administration errors. Proper flow of CSSD in the hospital setup can allow the pharmacists to prepare the dose and reduce errors. Prescription errors can be handled by emphasizing the importance of applying guidelines and training healthcare workers accordingly. (41)

Conclusions

This study sailed through the adversities caused by chemotherapeutic agents in the days of a patient's life. While wrapping up the study, a greater number of patients faced the adversities of GI symptoms. From head to toenails, chemotherapy has its side effects. Nevertheless, It has to always be associated with palliative care for patients. Drugs that are invented to heal should not make people's lives more miserable. It is at this point, we have to make sure that the treatment is received by the patient with the least number of errors. This study pointed out different areas in which medication adverse events could occur. Proper training programs like workshops and seminars along with assistance from various departments like nursing, and pharmacy in chemotherapeutic agent preparation could retard medication errors from occurring. This study was able to portray the relevance of doing so with evidence.

Acknowledgment

Upon completing this thesis, I would like to thank the almighty for gracing me with good health, courage, and inspiration.
I also extend my gratitude towards my guide, Dr. Shibi Mary Thomas, for encouraging me to complete the latter and I am grateful to my family for their prayers, blessings, and all the support they gave me throughout my life.

Reference

1. WHO Int WG for Drug Statistics Methodology. Introduction to Drug Utilization Research World Health Organization. Solutions. 2003.
2. Komagamine J, Kobayashi M. Prevalence of hospitalisation caused by adverse drug reactions at an internal medicine ward of a single centre in Japan: A cross-sectional study. BMJ Open. 2019 Aug 1;9(8).
3. Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. Br J Clin Pharmacol [Internet]. 2014 [cited 2022 May 6];78(2):202–17. Available from: https://pubmed.ncbi.nlm.nih.gov/24283967/
4. India Population below poverty line - Economy [Internet]. [cited 2022 May 6]. Available from: https://www.indexmundi.com/india/population_below_poverty_line.html
5. Rise and prevalence of Cancer in India - Times of India [Internet]. [cited 2022 May 6]. Available from: https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/rise-and-prevalence-of-cancer-in-india/articleshow/56969996.cms
6. Spandana A, Sneha KLK, Sandyapakula B, Kumar VT, Charan TK, Rahaman SA. a Study on Prevalence and Drug Utilization Pattern in Department of Oncology of Tertiary Care Hospital in India. Indo Am J Pharm Res [Internet]. 2017;7(04). Available from: www.iajpr.com
7. Treatment For Cancer | Cancer Treatment Options [Internet]. [cited 2022 May 6]. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types.html
8. Cancer chemotherapy and why correct dosing matters? [Internet]. [cited 2022 May 14]. Available from: https://news.cancerresearch/what-is-cancer-chemotherapy-and-why-correct-dosing-matters/
9. Chemotherapy Side Effects | American Cancer Society [Internet]. [cited 2022 May 14]. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/chemotherapy-side-effects.html
10. A medical oncologist explains the benefits and risks of chemotherapy | CTCA [Internet]. [cited 2022 May 26]. Available from: https://www.cancercenter.com/community/blog/2021/03/benefits-and-risks-of-chemotherapy
11. NIH study offers insight into why cancer incidence increases with age | National Institutes of Health (NIH) [Internet]. [cited 2022 Jun 3]. Available from: https://www.nih.gov/news-events/news-releases/nih-study-offers-insight-into-why-cancer-incidence-increases-age
12. Cancer [Internet]. [cited 2022 Jun 7]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
13. Common Chemotherapy Drugs - Health Hearty [Internet]. [cited 2022 Jun 7]. Available from: https://healthhearty.com/common-chemotherapy-drugs
14. The DNA adducts formed by the platinum-containing complexes inhibit DNA replication and lead to strand breaks and miscoding, thereby eliciting apoptosis as well as inhibition of RNA and protein synthesis.
15. Paclitaxel (Taxol) and docetaxel (Taxotere): active chemotherapeutic agents in lung cancer - PubMed [Internet]. [cited 2022 Jun 11]. Available from: https://pubmed.ncbi.nlm.nih.gov/7551925/
16. Microtubule inhibitors: Differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance - PubMed [Internet]. [cited 2022 Jun 11].
17. Available from: https://pubmed.ncbi.nlm.nih.gov/19671735/17. About Antitumor Antibiotics [Internet]. [cited 2022 Jun 11]. Available from: https://www.healthline.com/health/cancer/about-antitumor-antibiotics#types-of-antitumor-antibiotics18.

18. Nausea and Vomiting Related to Cancer Treatment (PDQ®)–Health Professional Version - NCI [Internet]. [cited 2022 Jun 14]. Available from: https://www.cancer.gov/about-cancer/treatment/side-effects/nausea/nausea-hp-pdq19. Chemotherapy-Induced Nausea and Vomiting [Internet]. [cited 2022 Jun 14].
19. Available from: https://www.uspharmacist.com/article/chemotherapyinduced-nausea-and-vomiting20. Chemotherapy-Induced Diarrhea [Internet]. [cited 2022 Jul 12]. Available from: http://www.oncology.tv/SymptomManagement/Chemotherapy-InducedDiarrhea.aspx21.
20. Why Does Chemotherapy Reduce Your Appetite?: ENU [Internet]. [cited 2022 Jul 12]. Available from: https://enu-nutrition.com/blog/why-does-chemotherapy-reduce-your-appetite/22. Was H, Borkowska A, Bagues A, Tu L, Liu JYH, Lu Z, et al. Mechanisms of Chemotherapy-Induced Neurotoxicity. Front Pharmacol. 2022 Mar 28;13:923.23.
21. Zajaczkowską R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. Int J Mol Sci [Internet]. 2019 Mar 2 [cited 2022 Jul 20];20(6).
22. Available from: /pmc/articles/PMC6471666/24. Staff NP, Cavaletti G, Islam B, Lustberg M, Psimaras D, Tamburin S. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst [Internet]. 2019 Oct 1 [cited 2022 Jul 25];24(Suppl 2):S26.
23. Available from: /pmc/articles/PMC6818741/25. Bryer E, Henry D. Chemotherapy-induced anemia: etiology, pathophysiology, and implications for contemporary practice. Int J Clin Transfus Med. 2018 Nov;Volume 6:21–31.26. Fang H, Xie X, Liu P, Rao Y, Cui Y, Yang S, et al. Ziyuglycoside II alleviates cyclophosphamide-induced leukopenia in mice via regulation of HSPC proliferation and differentiation.
24. Biomed Pharmacother. 2020 Dec 1;132:110862.27. Vadhan-Raj S. Management of Chemotherapy-Induced Thrombocytopenia: Current Status of Thrombopoietic Agents.
25. Semin Hematol [Internet]. 2009;46(SUPPL. 2):S26–32. Available from: http://dx.doi.org/10.1053/j.seminhematol.2008.12.00728. Tsai CJ, Wang SS, Ou YC.
26. Cyclophosphamide-induced intractable hemorrhagic cystitis treated with hyperbaric oxygenation and intravesical sodium hyaluronate. Urol Sci. 2014;25(4):155–7.29. Hair Loss (Alopecia) from Chemotherapy | OncoLink [Internet]. [cited 2022 Aug 10].
27. Available from: https://www.oncolink.org/support/side-effects/skin-hair-nail-side-effects/hair-loss-alopecia-from-chemotherapy30. Chemotherapy Side Effects | American Cancer Society [Internet]. [cited 2022 May 14]. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/chemotherapy-side-effects.html31.
28. Alshari O, Aleshawi A, Al Sharie AH, sameh A, Al-Omari I, Msameh R, et al. The Effect of Nail Lacquer on Taxane-Induced Nail Changes in Women With Breast Cancer. Breast Cancer: Basic and Clinical Research [Internet]. 2020 Jan;14:117822342092970.
29. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7297473/32. Pavey RA, Kambil SM, Bhat RM. Dermatological adverse reactions to cancer chemotherapy. Indian J Dermatol Venereol Leprol [Internet]. 2015 [cited 2022 Dec 6];81(4):434.
30. Available from: https://ijdvl.com/dermatological-adverse-reactions-to-cancer-chemotherapy/33. Rowden A. Fever during chemotherapy: Treatment, prevention, and support [Internet]. Medicalnewstoday.com. 2021 [cited 2022 Dec 6].
31. Available from: https://www.medicalnewstoday.com/articles/chemotherapy-fever34. College Basketball Star. Cancer patient balance issues [Internet]. Cancer Treatment Centers of America. 2018 [cited 2022 Dec 6].
32. Available from: https://www.cancercenter.com/integrative-care/balance35. Was H, Borkowska A, Bagues A, Tu L, Liu JYH, Lu Z, et al. Mechanisms of chemotherapy-induced neurotoxicity. Front Pharmacol [Internet]. 2022;13:750507.
33. Available from: http://dx.doi.org/10.3389/fphar.2022.75050736. Causes of sweating [Internet]. Cancerresearchuk.org. [cited 2022 Dec 6].
34. Available from: https://www.cancerresearchuk.org/about-cancer/coping/physically/skin-problems/dealing-with-sweating/causes37. Lee CS, Ryan EJ, Doherty GA. Gastro-intestinal toxicity of chemotherapeutics in colorectal cancer: the role of inflammation. World J Gastroenterol [Internet]. 2014 [cited 2022 Dec 6];20(14):3751–61.
35. Available from: http://dx.doi.org/10.3748/wjg.v20.i14.375138. Grigorian A, O'Brien CB. Hepatotoxicity secondary to chemotherapy. J Clin Transl Hepatol [Internet]. 2014 [cited 2022 Dec 7];2(2):95–102.
36. Available from: https://www.xiahepublishing.com/2310-8819/JCTH-2014-0001139. Knox J. What happens to your period after chemo? [Internet]. Verywell Health. 2021 [cited 2022 Dec 7].
37. Available from: https://www.verywellhealth.com/periods-after-chemo-519667440. Jabalpeikar S. Evaluation of the medication safety of chemotherapy drugs.
38. In: Herdeiro MT, Roque F, Figueiras A, Silva TM, editors. New Insights into the Future of Pharmacoepidemiology and Drug Safety.
39. London, England: IntechOpen; 2021.41. Goodin S, Griffith N, Chen B, Chuk K, Daouphars M, Doreau C, et al. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. J Oncol Pract [Internet]. 2011 [cited 2022 Dec 14];7(1):7–12. Available from: http://dx.doi.org/10.1200/jop.2010.000068