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A Review on Antineoplastic Agents Induced Toxicities and its Managements

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Abstract: ***Toxicities following use of antineoplastic agents tends to be the most significant barrier to the compliance of all modes of cancer therapy including those with curative intent. Proper anticipation of the numerous drug induced toxicities provide opportunities to develop interventional strategies to limit or eliminate the known adverse effect of the chemotherapy that if left unattended will decrease the treatment tolerability and overall quality of life. This abridged article provides an overview of the toxicities arising from the chemotherapeutic agents an its management.***

Keywords: Antineoplastic agents, Toxicities, Management

1. Introduction

Cancer is a disease caused by dysregulated clonal cell proliferation, leading to the formation of tumors. Systemic treatment of cancer ranges from various intravenous chemotherapy drugs either as single agent or in combination which may or may not be supplemented with immunotherapy. Radiotherapy and/or surgery forms a cornerstone of treatment in early cancer based on the type as well as extent of invasion of the cancers ([1]). Antineoplastic agents (Table1) are currently used as the primary treatment for advanced disease as well as for adjuvant therapy in local malignant tumors. This article gives a general overview of toxicity of chemotherapy including hematological toxicity, gastrointestinal toxicity, neurotoxicity, cardio toxicity, gonadal toxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity and sebaceous follicular toxicity leading to alopecia and dry skin ([2]).

Alkylating Agents		Alteramine	Bendamustine	Busulfan	Carmustine
		Chlorambucil	Cyclophosphamide	Dacarbazine	Ifosfamide
		Lomustine	Mechlorethamine	Melphalan	Procarbazine
		Streptozocin	Temozolomide	Thiotepa	Trabectedin
	Antifolates	Methotrexate	Pemetrexed	Pralatrexate	Trimetrexate
	Purine Analogues	Azathioprine	Cladribine	Fludarabine	Mercaptopurine
		Thioguanine			
	Pyrimidine Analogues	Azacitidine	Capecitabine	Cytarabine	Decitabine
		Floxuridine	Fluorouracil	Gemcitabine	Trifluridine
Platinum Coordination Complex		Carboplatin	Cisplatin	Oxaliplatin	
Cytotoxic Antibiotics		Bleomycin	Dactinomycin	Daunorubicin	Doxorubicin
		Epirubicin	Idarubicin	Mitoxantrone	Plicamycin
		Mitomycin	Valrubicin		
Vinca Alkaloids		Vincristine	Vinblastine	Vinorelbine	
Taxanes		Cabazitaxel	Docetaxel	Paclitaxel	
Topoisomerase I Inhibitors		Topotecan	Irinotecan		
Topoisomerase II Inhibitors		Etoposide	Teniposide		
Miscellaneous		L - Asparaginase	Bexarotene	Eribulin	Everolimus
		Hydroxyurea	Ixabepilone	Lenalidomide	Mitotane
		Omacertaxine	Pomalidomide	Tagraxofusp	Telotristat
		Temsirolimus	Thalidomide	Venetoclax	

Hematological Toxicity

Cytopenias or the decrease in the number of mature blood cells due to bone marrow suppression is one of the most frequent dose limiting side effects of chemotherapy. Chemotherapeutic agents destroy fast growing cells which include blood cells hence contributing to the delay in formation of formed elements in the blood. The bone marrow suppression is clinically presented in the form of neutropenia, anemia and thrombocytopenia ([2]). Common Terminology criteria for Adverse Event (CTCAE) grading for hematological toxicity ([3]) (Table 2)

Table 2: CTCAE grading for hematological toxicity

Common Terminology criteria for Adverse Event (CTCAE) grading for hematological toxicity			
Grading	Anemia Hemoglobin (g/ dL)	Neutropenia ANC (cells / µL)	Thrombocytopenia Platelets (cells / mm³)
Grade 1	<LLN – 10	>1500	LLN - 75000
Grade 2	<10 – 8	1000– 1500	<75000 – 50000
Grade 3	<8 – 6.5	500 – 1000	<50000 – 25000
Grade 4	<6.5	<500	<25000

Anemia

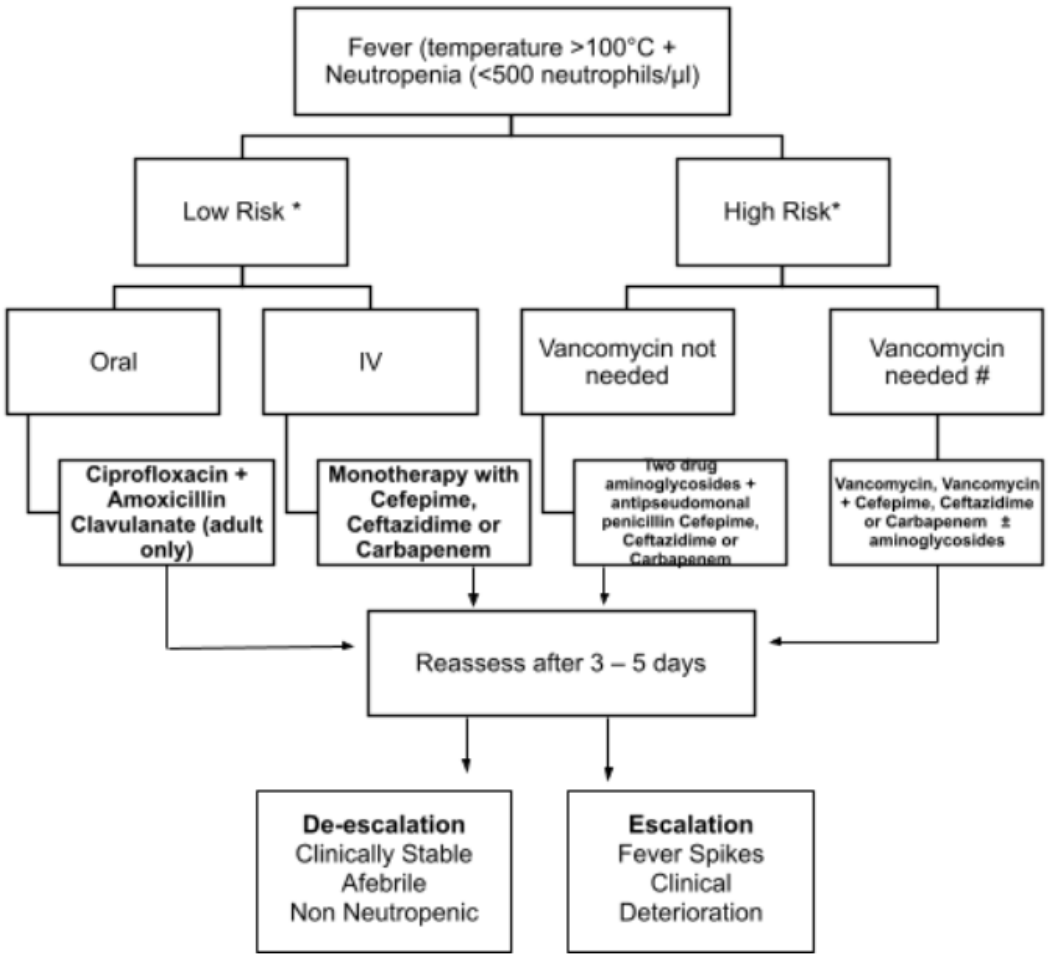
Anemia is defined for patient care as a reduction in one or more of the major red blood cell (RBC) measurements obtained as a part of the complete blood count (CBC) hemoglobin concentration, hematocrit or RBC count. It is often a manifestation of underlying conditions such as blood loss, iron deficiency, renal insufficiency, nutritional deficiency, hereditary disorders, hemolysis, cancer or anemia due to chronic disease, hematolymphoid malignancies with marrow infiltration and occasionally due to bone marrow infiltration by solid tumors [4]. The clinical diagnosis is established based on CBC, reticulocyte count, RBC indices, morphology from Peripheral Smear examination and ancillary studies like stool occult blood, serum iron, Vitamin B12, total iron binding capacity, transferrin saturation, folic acid level, Direct Coombs test (DCT) as well as bone marrow evaluation. Hematinic /Iron supplements and Vitamin B12, Folate, iron rich diet is the first line management if Iron deficiency is demonstrated. Erythropoietin stimulating agents are preferred in symptomatic patients with anemia due to chronic disease where rapid correction is not required. (Example. Recombinant human Erythropoietin, Darbepoetin Alfa, Epoetin Alfa, Epoetin Beta). Blood transfusion is preferred for immediate correction in symptomatic patients (Tachycardia, Tachypnea) [5].

Neutropenia

Neutropenia is defined as an ANC of <500 cells/mm3 or an ANC that is expected to decrease to <500 cells/mm3 during the next 48 hrs. Neutrophil counts usually drop to its lowest level on day 7 - 14 post chemotherapy which is commonly referred to as nadir. [6] Absolute Neutrophil count (ANC) is a measure of the number of neutrophils in the blood which helps in providing a rough estimate of the ability to fight infection. ANC is calculated by multiplying WBC count to the percentage of neutrophils in the blood. Granulocyte Colony Stimulating Factor (GCSF) or PEGylated G CSF may be used as Primary prophylaxis in patients older than 65 years. Chemotherapy regimen where 10 - 20 % febrile neutropenia is expected and other high risk populations [7].

Febrile Neutropenia

Febrile Neutropenia a life threatening condition defined by an oral temperature > 38.3ºC (101 ºF) from a single reading or temperature of > 38.0 ºC (100.4 ºF) sustained over a 1 - hour period or reported from 2 consecutive readings in a 2 - hour period and an ANC <0.5 x 10^9/l or expected to fall below <0.5 x 10^9/l [8]. Management of febrile neutropenia involves appropriate use of antimicrobials with supportive measures till symptomatic relief and count recovery ([9] (Figure 1)



* Risk stratification based on MASCC Index
# Indicated in suspected catheter related infection, skin and soft tissue infection, pneumonia or hemodynamic instability

Figure 1: Treatment algorithm for the management of febrile neutropenia

Thrombocytopenia

Thrombocytopenia is a condition in which there is a low number of blood platelet counts. A moderate risk of bleeding exists when the platelet count falls to less than 50000 cells/ mm^3 and major risk of bleeding may be anticipated when the platelet count falls to less than 10000 cells/ mm^3. Clinical manifestations include bruising, purpura, ecchymosis or mucosal bleed and may even progress to organ bleed from CNS, lungs or GI region ([10]). Mild to moderate thrombocytopenia may be managed symptomatically by platelet transfusion (4 - 6 units of random donor platelet or 1 single donor platelet). Thrombopoietin receptor agonist such as Eltrombopag, Romiplostim etc. maybe considered for patients with aplastic anemia, relapsed refractory thrombocytopenia after treatments with steroids, immunoglobulin or splenectomy ([11]).

Gastrointestinal Toxicities

Diarrhea

Chemotherapy induced diarrhea typically involves increased frequency of bowel movements and/or loose watery stool which may or may not be accompanied by intestinal cramps or excessive flatulence which may cause extreme dehydration and fatigue ([12]).

Chemotherapy related Diarrhea (CRD) typically occurs through three primary mechanisms:

1) Increased electrolyte secretion by luminal secretagogues or reduced absorptive capability from loss of absorptive surfaces due to damage to intestinal mucosa called as secretory diarrhea
2) Increased intraluminal osmotic substances leading to osmotic diarrhea, or
3) Altered GI motility.

CRD is most typical with fluoropyrimidines particularly 5 - Fluorouracil, Capecitabine and Irinotecan.5 - Fluorouracil administration with Leucovorin, increases the therapeutic effects as well as diarrhea associated with it ([13]). Delayed diarrhea is often unpredictable, non - cumulative and can occur at any dose. In addition to traditional chemotherapy, proteasome inhibitors such as Bortezomib, Tyrosine kinase inhibitors and other targeted therapies also induce diarrhea. Among the molecularly targeted agents linked to CRD, the most common are of tyrosine - kinase inhibitors (TKIs) targeting the epidermal receptor of the growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2) in particular, Neratinib and Afatinib, CDK4/6 inhibitor like Abemaciclib, combinations of MEK and BRAF inhibitors such as Trametinib / Dabrafenib, anaplastic lymphoma kinase (ALK) inhibitors such as Ceritinib, the Bruton tyrosine kinase (BTK) inhibitor Ibrutinib and the phosphoinositide 3 - kinase (PI3K) inhibitors Idelalisib, Duvelisib and Alpelisib ([12, 13]). Diarrhea typically responds to antidiarrheal therapy along with sufficient hydration and treatment discontinuation is rarely needed. Even though both loperamide and diphenoxylate - atropine are effective at controlling acute and chronic diarrhea, loperamide is recommended for initial therapy of CRD. Octreotide, a synthetic somatostatin analog, is effective for the control of secretory diarrhea. Racecadotril is an enkephalinase inhibitor that blocks epithelial cyclic adenosine monophosphate (AMP) - mediated secretion that has moderate activity in patients with Irinotecan - induced diarrhea ([14]).

Patients undergoing chemotherapy may also develop diarrhea due to infection especially while neutropenic and several type of colitis which include neutropenic enterocolitis, ischemic colitis, *Clostridium difficile* - associated colitis**,** lymphocytic colitis, Pseudomonas colitis or immune related colitis maybe seen with immune related drugs ([15]).

Constipation

Constipation is rarely a dose - limiting toxicity for chemotherapeutic agents except in case of Vinca alkaloids, particularly Vincristine and is common with Lenalidomide and its related drugs like Thalidomide and Pomalidomide. Though severe constipation is uncommon, anticipation should be the goal of treatment with initiation of laxatives at first sign of constipation or on a regular basis to prevent constipation. Constipation treatment begins with anticipation and prevention with increased fluid intake and use of osmotic laxatives (containing Polyethylene glycol, Lactulose) stimulant laxative (Bisacodyl, Senna) and encouraging dietary fibers or supplements ([16]).

EMESIS

Gastrointestinal (GI) toxicity is a common complication of cytotoxic cancer chemotherapy with nausea and vomiting being the most cited effect after chemotherapy. Its severity varies from patient to patient based on drug, its dose, patient tolerance and may range from mild nausea to persistent vomiting with subsequent dehydration ([17]). The chemotherapy - induced nausea and vomiting (CINV) is not a pathological process, but a physiological process in which the human body tries to get rid of toxic substances. This response is controlled by a reflex (coordination zone) with multiple afferent limbs. Vomiting center and multiple efferent pathways to activate and coordinate the muscle groups required for a successful emetic response. The afferent limbs include;

1) Chemoreceptor Trigger Zone (CTZ) pathway, through which substances are released into the cerebrospinal fluid thus activating the trigger zone.
2) Peripheral pathways, which are activated by the corresponding neurotransmitter receptors through the vagus nerve.
3) Spinal corticosteroid pathways.

It is categorized as acute, delayed, and anticipatory and has important implications for the management of patients. Individual Chemotherapeutic agents or combinations are classified into highly emetogenic (>90% risk of emesis), moderately emetic (30 - 90 % risk of emesis), low emetic (10 - 30% risk of emesis) or minimally emetic (<10 % risk of emesis) according to their emetogenic potential. For combination regimens, the emetic level is determined by identifying the most emetic agent in the combination and then assessing the relative contribution of the other agents ([18]).

Despite remarkable advances in prevention of chemotherapy - induced nausea and vomiting (CINV), it continues to have a significant impact on cancer treatment.5 - hydroxytryptamine (5 - HT3) receptor antagonists (Ondansetron, Palanosetron, Granisetron), neurokinin - 1 receptor (NK1R) antagonists (Aprepitant, Fosaprepitant, Neupitant), and glucocorticoids (Dexamethasone) are among the three group of medication with higher spectrum of activity for chemotherapy induced nausea and vomiting [17, 18]. Olanzapine, an atypical antipsychotic agent having the ability to block different receptors including dopaminergic, serotonergic, adrenergic, histaminergic, muscarinic receptors also provides antiemetic properties. Dopamine antagonists (Metoclopramide, Domperidone) and antihistamine (Promethazine, Meclizine) may also be used in addition to other antiemetic drugs. These agents are used alone or in combinations according to the emetogenicity of the chemotherapy regimen being administered and its tendency to produce not only acute but also delayed emesis. [16, 19]. Common Terminology criteria for Adverse Event (CTCAE) grading for gastrointestinal toxicity ([3]) (Table 3)

Table 3: Common Terminology criteria for Adverse Event grading for gastrointestinal toxicity

	Mucositis	Nausea	Vomiting	Diarrhea	Constipation
Grade 1	Asymptomatic or mild symptoms; intervention not indicated.	Loss of appetite without alteration in eating habits	Intervention not indicated	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Intermittent symptoms, occasional use of laxative/enemas
Grade 2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated.	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Outpatient intravenous hydration; medical intervention indicated	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental activities of daily living (ADL)	Persistent symptoms with regular use of laxatives /enemas
Grade 3	Severe pain; interfering with oral intake.	Inadequate oral caloric or fluid intake; tube feedings, TPN, or hospitalization indicated	Tube feeding, TPN, or hospitalization indicated	Increase of seven or more stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; Limiting self - care ADL	Obstipation with indication for manual evacuation
Grade 4	Life – threatening consequences; urgent intervention indicated.	-	Life – threatening consequences	Life – threatening consequences; urgent intervention indicated.	Life - threatening consequences; urgent intervention indicated.

Mucositis

In patients on chemotherapy there may be possibility for damage to the normal proliferation of the epithelial lining along with delay in the rate of renewal of mucosal lining. This may lead to oral ulceration, stomatitis, dysphagia, diarrhea, esophagitis, proctitis as well as any other inflammation with redness, pain and hemorrhage ([20]). Patients with hematological malignancy receiving intensive chemotherapy and all those receiving myeloablative conditioning regimen prior to hematopoietic stem cell transplant are at high risk of getting Mucositis.

Uncomplicated Mucositis is generally self - limiting and the symptoms may be managed with supportive care till the mucosa becomes normal. Salt and soda bicarbonate mouth gargles is an inexpensive, safe and effective method for treatment of mucositis and may also be used as a prophylaxis measure and can provide relief in case of mild to moderate Mucositis pain. [17] Topical anesthetics, such as 2 % viscous lidocaine gargle aid in providing topical anesthesia but can numb the entire mouth with care needed to avoid inadvertent tongue bites. Prophylaxis may be given in the form of oral Clotrimazole lozenges as well as Acyclovir against viral infection but secondary oral Mucositis infection needs appropriate treatment with topical or systemic antifungal therapy ([20]). Common Terminology criteria for Adverse Event (CTCAE) grading for gastrointestinal toxicity ([3]) (Table 4)

Table 3: CTCAE grading for Peripheral neuropathy and HFS

	Peripheral neuropathy	HFS
Grade 1	Asymptomatic; clinical or diagnostic observations only.	Minimal skin changes or dermatitis without pain.
Grade 2	Moderate symptoms; limiting instrumental activities of daily living.	Skin changes with pain; limiting instrumental activities of daily living
Grade 3	Severe symptoms; limiting self - care activities of daily living	Severe skin changes with pain; limiting self - care activities of daily living
Grade 4	Life threatening consequences; urgent intervention indicated.	-

Renal & Urinary Toxicity

The risk for renal toxicity in cancer patients increases with age, concomitant use of other nephrotoxic drugs, dietary status and pre - existing renal dysfunction. The most critical and fatal complications are acute renal failure and hemolytic uremic syndrome, but are uncommon. [18]. Common nephrologic parameters evaluated prior to treatment are the blood urea nitrogen concentration, serum creatinine and electrolytes which are then periodically repeated before each chemotherapy. Chemotherapy is dose adjusted to prevent or minimize the renal toxicity [21, 22]. The accumulation of Cisplatin as well as its biotransformation to a highly reactive platinum thiol in the kidneys may lead to renal dysfunction. The alleviation of Cisplatin induced renal toxicity is presently carried out by hydration, Potassium and magnesium supplementation along with addition of diuretics if needed [23]. Gemcitabine is associated with a potentially lethal condition called Hemolytic Uremic syndrome (HUS) which is a progressive renal failure associated with

microangiopathic hemolytic anemia and thrombocytopenia that initiates with damage to endothelial cells. It requires early diagnosis with prompt treatment starting with immediate discontinuation of the drug along with steroids, transfusions, dialysis, plasmapheresis with or without use of Rituximab. Cyclophosphamide and Ifosfamide produce a corrosive liver m - metabolite called acrolein that is freely filtered by the kidneys which then get accumulated in the bladder [24]. Acrolein causes a pyrophoric reaction in the bladder urothelium which then often presents with ulceration and exposure of underlying muscularis mucosa and vasculature. An Acrolein conjugator called Mesna (2 – mercaptoethane sulfonate sodium) which acts by binding to and neutralizing acrolein may be utilized as prophylaxis. Mesna is not useful in the treatment of hemorrhagic cystitis after its onset. The use of Mesna before initiation of either Ifosfamide or high dose Cyclophosphamide along with adequate hydration significantly reduce the incidence of hemorrhagic cystitis ([24, 25]. There are many mechanisms that describe Methotrexate nephrotoxicity but the most common one is the proposal of crystallization of Methotrexate in the renal tubular lumen. The current standard for management of Methotrexate induced nephrotoxicity includes prophylactic intravenous hydration, alkalization of urine with the aid of Sodium bicarbonate +/ - Disodium hydrogen citrate and appropriate Leucovorin rescue. Patients with infectious cystitis typically present with irritative voiding symptoms, dysuria or suprapubic pain but gross hemorrhage is also a rare presentation. Alternative treatment modalities include bladder irrigation with evacuation of clots, hyperbaric oxygen therapy, and severe conditions, cystectomy with urinary diversion ([26].

Hepatotoxicity

Most subjects undergoing chemotherapy have exposure to hepatotoxins from chemotherapeutic agents along with hepatic impairment due to other medication, alcohol or even coexistent liver disease. Hepatic Parameters such as bilirubin levels, liver enzymes like SGOT, SGPT, ALP, GGT, Prothrombin Time etc. must be evaluated prior to and before each chemotherapy to monitor liver functioning. Chemotherapy must be dose adjusted to prevent or minimize the hepatic toxicity ([22]. Hepatotoxicity reactions have an exceedingly varied pattern including parenchymal cell injury with necrosis, fibrosis, ductal injury with cholestasis and veno occlusive disease. Oxaliplatin induced sinusoidal obstruction syndrome (earlier known as veno occlusive disease) caused due to deposition of fibrous materials into small branches of hepatic veins causing obstruction, sinusoidal dilatation and hepatocellular lesions. It is treated with appropriate fluid management by avoiding excessive fluid loss as well as avoiding rapid diuresis, use of anticoagulants, steroids and ursodeoxycholic acid ([27].

Veno Occlusive disease of liver caused by any drug may be reversed by Defibrotide. Depending upon patient clinical status and extent of hepatic impairment we may consider dose reduction of chemotherapy, intermittent therapy and discontinuation of drug along with necessary supportive management.

Cardiac Toxicity

Cardiotoxicity may appear early on, during or even after therapy, with presentation varying from subclinical myocardial dysfunction to irreversible heart failure. Evaluation of the cardiac functioning of the patient either using Echocardiogram or Multigated Acquisition Scan (MUGA) along with Electrocardiogram (ECG) must be done to obtain a baseline as well as periodically till the end of treatment [28]. Anthracycline induced mitochondrial damage, changes in ATP production, and cellular apoptosis, along with increase in production of free radical species that affects the cardiomyocyte. Trastuzumab dysregulates HER2 signaling and suppresses autophagy in cardiomyocytes to trigger accumulation of toxic reactive oxygen species (ROS) in human cardiomyocytes thereby compromising their ability to recycle toxic cellular substrates causing cardiotoxicity [29, 30]. Cardiac toxicity is mainly of three types the first being acute toxicity that occurs within hours of drug administration presenting with arrhythmia, sinus tachycardia, ECG changes. Subacute toxicity occurs within weeks to months after therapy or within one year of therapy. Late onset toxicity occurs one to five years after treatment. Management of cardiac toxicity can be done efficiently with early detection and supportive therapy. Use of Beta – blockers with antioxidant properties, such as Carvedilol as prophylaxis may aid to reduce the risk of cardiotoxicity in patients requiring exposure to cardio toxic chemotherapy. [30] The management may also be done using iron cheaters such as Dexrazoxane which hydrolyzes to its active form intracellularly and binds iron to prevent the formation of superoxide radicals, thus preventing mitochondrial destruction. [29]

Pulmonary Toxicity

Some chemotherapeutic agents can damage epithelial or endothelial lung tissue. Clinical manifestation of pulmonary toxicity includes lung fibrosis, acute pneumonitis, non - cardiogenic pneumonitis and pulmonary edema ([31]. Pulmonary status of the patient must be assessed using Pulmonary function test (PFT) with Diffusing capacity for Carbon monoxide (DLCO) prior to use of chemotherapy with known pulmonary toxicity as well as in regular intervals along with monitoring for any alteration in respiratory capacity. Among the traditional chemotherapy Pulmonary toxicity is caused by Bleomycin which involves the oxidative damage, relative deficiency of the bleomycin hydrolase, genetic susceptibility and the amplification of inflammatory cytokines ([32]. In addition Interstitial Lung Disease can be induced by Tyrosine Kinase Inhibitors Eg: Gefitinib. Immunotherapy agents can incite immune mediated pneumonitis which need early identification and corticosteroids/ other immunosuppressive agents. Prompt treatment includes discontinuation of the drug and administration of corticosteroids and supportive care.

Gonadal Toxicity

The effects of radiotherapy and traditional chemotherapy regimen on gonads are well described in the literature; however, the growing profusion of modern chemotherapies, immunotherapies, targeted therapies currently in routine use are often poorly validated for its gonadal toxicity.

In women chemotherapy affects the primordial follicle pool, damage ovarian cortex and reduce ovarian blood flow leading to early exhaustion of ovarian follicle stockpile and premature ovarian failure thus diminishing fertility or potential to conceive. Most devastating consequences of chemotherapy in the young population is irreversible ovarian damage leading to permanent sterility and early menopause [33]. The choice of fertility preservation techniques depends on age, chemotherapy protocol, duration and cumulative dose administered. Premature menopause which is yet another complication of chemotherapy can be treated with hormone replacement. [29] The use of pharmacologic prevention using Gonadotropin release hormone (GnRH) agonist along with chemotherapy may reduce premature ovarian failure thus offering a benefit of ovarian suppression during chemotherapy. In addition Embryo cryopreservation, Oocyte cryopreservation can be attempted in selected patients. The option of surrogacy also may be explored; however the medico - legal and legal implications have to be reviewed as relevant to each country.

As Spermatogenesis is highly sensitive to the effect of chemotherapy and irradiation, male patients should, if relevant, be offered suggestions of sperm banking before initiation of treatment. Testicular Biopsy and cryopreservation may be resorted to if needed. Testosterone deficiency, another less common reproductive toxicity with chemotherapy can often be easily corrected with testosterone replacement [34].

Central Nervous System (CNS) Toxicity

Chemotherapy may have significant effects either on central (CNS) or peripheral nervous system (PNS) which ranges from acute cerebral dysfunction, myelopathy, neurovascular syndromes, cognitive impairment to acute, subacute and chronic encephalopathies. The acute toxicity to the CNS may be caused by any agent (like Cisplatin, Cytarabine, Cyclophosphamide, Methotrexate, Fluorouracil, Vinblastine) that crosses the blood brain barrier with ease which in turn results in excitatory mechanisms and apoptotic cell death. The cerebrovascular risk is also common in medications like Doxorubicin, Methotrexate and platinum - based treatments.

Acute encephalopathy may develop within a few hours to days after administration of Methotrexate and Ifosfamide with presenting complaints of disorientation, confusion, agitation, myoclonic jerks, seizures and hallucinations symptoms and eventually coma. Ifosfamide and its metabolites act by interfering in thiamine function hence intravenous thiamine may be used as prophylaxis to prevent it [35].

High dose Cytarabine and Methotrexate may account to cerebral dysfunction and neurotoxicity respectively which may be altered by drug excretion with adequate hydration, urinary alkalinisation and use of Leucovorin rescue. This characteristic syndrome begins with somnolence which may progress into encephalopathy that develops two to five days after beginning treatment [36]. The use of Aminophylline in methotrexate induced acute encephalopathy may be useful. The disruption of the microtubules within axons and interference with axonal transport is the dose limiting toxicity of Vincristine for which symptoms range from mild ataxia to an inability to sit or walk unassisted. Whereas drugs like L - asparaginase increases risk of venous sinus thrombosis.

In case of lack of specific treatment or preventive measure the drug should be withheld temporarily, dose decreased or discontinued immediately. In some patients, the syndrome resolves spontaneously, but it is permanent in others. Chemotherapy induced Cognitive impairment (CICI) also known as Chemo brain or Chemo fog is defined as the impairment in patients‘ memory, learning, concentration, reasoning, executive functioning, attention and visuospatial skills during and after discontinuation of chemotherapy. CICI is commonly associated with drugs like Doxorubicin, Cisplatin, Cyclophosphamide, Cytarabine, 5 - Fluorouracil and Methotrexate and negatively affects patients quality of life but maybe improved with physical therapy and occupational therapy [37].

Peripheral Neuropathy (Nervous System Toxicity)

Peripheral neuropathy is a dose limiting effect of chemotherapy with sensory or motor symptoms appearing symmetrically in a stocking - glove shaped distribution pattern. It may involve;

1) Sensory Impairment: Numbness / Tingling, Neuropathic pain, increased sensibility to hot/cold temperatures, decreased vibration and pin prick sensitivity.
2) Motor Symptoms: Hyporeflexia, weakness and muscle cramps
3) Autonomic symptoms: dizziness, obstipation and orthostatic hypotension

Periwinkle plant derivatives (Vinca alkaloids) are a prominent anti neoplastic agent that has dose limiting neurotoxicity with symptoms including paresthesia of hands and feet, loss of deep tendon reflexes and weakness [38]. Thalidomide in patients with multiple myeloma reported severe (grade 3 or 4) peripheral neurotoxicity in approximately one - third of patients who received daily doses of >200 mg whereas Thalidomide derivative such as Lenalidomide and Pomalidomide appear to be less neurotoxic Common Terminology criteria for Adverse Event (CTCAE) grading for Peripheral motor neuropathy [3] (Table 3). The management involves discontinuation of the chemotherapeutic agent suspected as the cause for toxicity. These are mostly reversible if detected early and more frequent among older patients with risk increased with diabetes, alcoholic abuse and people with inflammation [39]. Although there are many risk factors linked with chemotherapy induced peripheral neuropathy, the most prevalent one is diabetes mellitus which can lead to major complications. Permanent neurological damage may be prevented by early detection and treatment of neurotoxicity, by reduction of further dose of the drug or discontinuation of the specific chemotherapeutic agent. [40] Tricyclic antidepressants, anticonvulsants and high dose vitamins are used in the treatment with Duloxetine being a specific agent for treatment of neuropathy [41].

Hand Foot Syndrome

Hand foot syndrome (HFS), also known as palmar – plantar erythrodysesthesia syndrome is usually characterized by

palmoplantar numbness, burning pain, drying, swelling or tingling often coinciding with sharply demarcated erythema with or without edema, cracking, or desquamation and vesiculation of the hands and feet [42]. Drugs causing hand foot syndrome liposomal Doxorubicin, Docetaxel, Capecitabine, Lapatinib and 5 - Fluorouracil. Hand - foot syndrome. Common Terminology criteria for Adverse Event (CTCAE) grading for HFS [3] (Table 3). Treatment is mostly focused towards symptomatic control. If there's swelling or inflammation, topical steroid creams may be prescribed ([43]. Sometimes the dose of the chemotherapy is also adjusted so as to manage further side effects [44]. Prophylactic use of moisturizers may alleviate dryness and medicated creams with urea can help get rid of rough skin. Use of urea based moisturisers as prophylaxis with Capecitabine reduces HFS incidence and severity

Temporary Alopecia / Hair Follicle Toxicity

Hair follicles have tissues and cells with rapid metabolic and mitotic rates hence they get affected by the antineoplastic agent along with the neoplastic cells [37]. The rapid hair growth and high blood flow rate around the hair bulb lead to the accumulation of drugs thus contributing towards the rapid and extensive alopecia. Hair fall starts as early as 1 to 2 weeks after the treatment due to the weakening and breakage of the hair shaft. [3 The use of cooling caps (cold caps) or cooling of scalp using ice packs to invoke scalp hypothermia before, during and after each chemotherapy help prevent/ reduce hair loss [45]. It involves tightly fitting helmet - like hats filled with cold gel or liquids that work by inducing vasoconstriction thus reducing blood flow to the hair follicles particularly during peak plasma concentration of chemotherapy used. It thus reduces the intensity of the chemotherapy on the hair follicles and makes it less susceptible to damage from it. Alopecia induced by chemotherapeutic agents is reversible and usually hair regrows normally after completion of chemotherapy [46].

2. Conclusion

Chemotherapeutic agents affect cells within the body having rapid turnover or innate potential to grow new cells since chemotherapy are unable to distinguish between them and cancerous cells. The effect of chemotherapy on such normal cells such as bone marrow, hair follicles, gastrointestinal mucosa etc. causes the various side effects that affect quality of life of chemotherapy patients. Such toxicity includes hematological toxicity, gastrointestinal toxicity, nephrologic toxicity, hepatic toxicity, neurotoxicity, gonadotoxicity, cardiac toxicity, pulmonary toxicity, sebaceous follicular toxicity leading to alopecia and dry skin. The toxicity involved may be reversible or irreversible but the focus of treatment will be to achieve reduction in tumor burden with appropriate prophylactic as well as symptomatic management for the toxicity anticipated based on the chemotherapy and its dose used. Information regarding the agents used with regards to toxicity, Anticipation of adverse effects, Preventive measures forms the most effective strategy. In addition, recognition of early toxicity symptoms and signs along with initiation of appropriate therapy will go a long way in avoiding chemotherapy dose reductions, chemotherapy discontinuation and non - compliance. The effective chemotherapy is not one without any toxicity but it involves proper management of the side effects while ensuring optimal dosage of chemotherapy is given to the patient. The management when done properly will ensure prolonged remission or prolonged progression free survival with tolerable quality of life for the patient during chemotherapy.

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References

[1] Repetto L. Greater risks of chemotherapy toxicity in elderly patients with cancer. J Supportive Oncol.2003; 1 (2): 18 - 24.
[2] Ishikawa A, Ohara G, Nakazawa K, Tamura T, Sato S, Kagohashi K, Kurishima K, Ito Y, Satoh H. Chemotherapy - induced complications in patients with lung cancer: An evaluation by pharmacists. Mol Clin Oncol.2013; 1 (1): 65 - 68.
[3] Rusu RA, Sîrbu D, Curşeu D, et al. Chemotherapy - related infectious complications in patients with Hematologic malignancies. J Res Med Sci.2018; 23: 68.
[4] Peters BG. An overview of chemotherapy toxicities. Top Hosp Pharm Manage.1994 Jul; 14 (2): 59 - 88.
[5] Bryer E, Henry D. Chemotherapy - induced anemia: etiology, pathophysiology, and implications for contemporary practice. International Journal of Clinical Transfusion Medicine.2018; 6: 21 - 31.
[6] Jerome E. Groopman, Loretta M. Itri, Chemotherapy - Induced Anemia in Adults: Incidence and Treatment, JNCI: Journal of the National Cancer Institute.1999; 91 (19): 1616–1634.
[7] Shayne M, Culakova E, Poniewierski MS, et al. Dose intensity and hematologic toxicity in older cancer patients receiving systemic chemotherapy, Cancer, 2007; 110: 1611–20.
[8] Crawford J, Dale DC, Kuderer NM, et al., Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice, J Natl Compr Canc Netw, 2008 (l6): 109–18.
[9] Lustberg MB. Management of neutropenia in cancer patients. Clin Adv Hematol Oncol.2012; 10 (12): 825 - 826.
[10] Kuter DJ. General aspects of thrombocytopenia, platelet transfusions, and thrombopoietic growth factors. In: Kitchens C, Kessler C, Konkle B, editors. Consultative Hemostasis and Thrombosis. Philadelphia: Elsevier Saunders.2013: 103 - 16.
[11] Hitron A, Steinke D, Sutphin S, et al. Incidence and risk factors of clinically significant chemotherapy - induced thrombocytopenia in patients with solid tumors. J Oncol Pharm Pract 2011; 17: 312 - 9.
[12] Maroun JA, Anthony LB, Blais N, et al. Prevention and management of chemotherapy - induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian working group on chemotherapy - induced diarrhea. Curr Oncol.2007; 14: 13 - 20.
[13] Boussios, Stergios et al. Systemic treatment - induced gastrointestinal toxicity: incidence, clinical presentation

and management. Annals of gastroenterology.2012; 25 (2): 106 - 118.
[14] Sharma, R obin P, Clarke SJ. Management of chemotherapy - induced nausea, vomiting, oral mucositis, and diarrhoea. Lancet Oncol.2005; 6: 93 - 102.
[15] Andreyev HJN, Davidson SE, Gillespie C et. al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut 2012; 61: 179–192.
[16] Sharma R, Tobin P, Clarke SJ. Management of chemotherapy - induced nausea, vomiting, oral mucositis, and diarrhoea. Lancet Oncol.2005; 6: 93 - 102.
[17] Navari RM. Management of chemotherapy - induced nausea and vomiting in pediatric patients. Pediatr Drugs 2017; 19: 213–222.
[18] Sharbaf FG, Farhangi H, Assadi F. Prevention of Chemotherapy - Induced Nephrotoxicity in Children with Cancer. Int J Prev Med.2017; 8: 76.
[19] Oh GS, Kim HJ, Shen A et al. Cisplatin - induced Kidney Dysfunction and Perspectives on Improving Treatment Strategies. Electrolyte Blood Press.2014; 12 (2): 55 - 65.
[20] Stillwell TJ, Benson RC Jr. Cyclophosphamide - induced hemorrhagic cystitis. A review of 100 patients. Cancer.1988 Feb 1; 61 (3): 451 - 7.
[21] Ritchey M, Ferrer F, Shearer P, Spunt SL. Late effects on the urinary bladder in patients treated for cancer in childhood: a report from the Children's Oncology Group. Pediatr Blood Cancer.2009; 52 (4): 439 - 446.
[22] Tanaka T, Nakashima Y, Sasaki H et al. Severe Hemorrhagic Cystitis Caused by Cyclophosphamide and Capecitabine Therapy in Breast Cancer Patients: Two Case Reports and Literature Review. Case Rep Oncol 2019; 12: 69 - 75.
[23] Grigorian A, O'Brien CB. Hepatotoxicity Secondary to Chemotherapy. J Clin Transl Hepatol.0; 2 (2): 95.
[24] Thatishetty AV, Agresti N, O'Brien CB. Chemotherapy - induced hepatotoxicity. Clin Liver Dis.2013 Nov; 17 (4): 671 - 86.
[25] Brown TJ, Sedhom R, Gupta A. Chemotherapy - Induced Peripheral Neuropathy. JAMA Onco*l.*2019; 5 (5): 750.
[26] Zajączkowska R, Kocot - Kępska M, Leppert W et al. Mechanisms of Chemotherapy - Induced Peripheral Neuropathy. *I*nt J Mol Sci.2019; 20 (6): 1451.
[27] Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, et al. Efficacy of gabapentin in the management of chemotherapy - induced peripheral neuropathy: a phase 3 randomized, double - blind, placebo - controlled, crossover trial (N00C3). Cancer.2007; 1109: 2110–8.
[28] Bhagra A, Rao RD. Chemotherapy - induced neuropathy. Curr Oncol Rep.2007 Jul; 9 (4): 290 - 9.
[29] Meirow, M Dror, Biederman et. al. toxicity of chemotherapy and radiation on female reproduction, clinical obstetrics and gynecology.2010; 53 (4): 727 - 739.
[30] Caroline M Allen, Federica Lopes, Rod T Mitchell et al. Comparative gonadotoxicity of the chemotherapy drugs cisplatin and carboplatin on prepubertal mouse gonads. Molecular Human Reproduction.2020; 26 (3): 129 - 140.
[31] Trapani D, Zagami P, Nicolo E et al. Management of cardiotoxicity induced by chemotherapy. Journal of clinmical medicine.2020 Sep; 9 (9): 2885.
[32] Florescu M, Cinteza M, Vinereanu D. Chemotherapy - induced Cardiotoxicity. Maedica (Bucur).2013; 8 (1): 59 - 67.
[33] Truong J, Yan AT, Cramarossa G, Chan KK. Chemotherapy - induced cardiotoxicity: detection, prevention, and management. Can J Cardiol.2014; 30 (8): 869 - 78.
[34] Abid SH, Malhotra V, Perry MC. Radiation - induced and chemotherapy - induced pulmonary injury. Curr Opin Oncol.2001 Jul; 13 (4): 242 - 8.
[35] utillas JR, Rodríguez EG, Viñals NB. Chemotherapy - induced pulmonary toxicity in lung cancer management. Revista de Oncología.2001; 3 (4): 183 - 195.
[36] Lemieux J, Maunsell E, Provencher L. Chemotherapy - induced alopecia and effects on quality of life among women with breast cancer: a literature review. Psychooncology.2008; 17: 317–28.
[37] Grevelman EG, Breed WPM. Prevention of chemotherapy - induced hair loss by scalp cooling. Ann Oncol.2005; 16: 352–8.
[38] Kwakman JJM, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy - induced hand - foot syndrome. Oncol Rev.2020; 14 (1): 442.
[39] Scheithauer W, Blum J. Coming to grips with hand - foot syndrome. Insights from clinical trials evaluating capecitabine. Oncology.2004; 18 (9): 1161 - 1184.
[40] Bardia A, Loprinzi CL, Goetz MP. Hand - foot syndrome after dose - dense adjuvant chemotherapy for breast cancer: a case series. J Clin Oncol.2006; 24 (13): e18 - e19.