



**LET'S MAKE CANCER CHEMOTHERAPY SAFE: A REVIEW ON ANTICANCER DRUGS RELATED TOXICITIES AND THEIR MANAGEMENT**

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**ABSTRACT**

One of the important consideration to treat cancer is anticancer drug therapy but standard antineoplastic therapy is associated with immunosuppression, infections and system related toxicities, some of the recent approaches can even induce overwhelming inflammation and autoimmunity. Even newly approved anticancer drugs that do not have a specific molecular target on cancer cells are not free from side effects, they are associated with increased toxicity and the accompanying costs of management. Until the newer anticancer drugs are being discovered with either no or very few toxicities, the available techniques and knowledge can be used to minimise them. This review article is throwing some light on predictable toxicities related to anticancer drugs, their management and prevention strategies, so their occurrence can be minimised and helped to tolerate them well.

**KEYWORDS:** Anticancer Drugs, Toxicities, Oncology, Chemotherapy, Radiotherapy, Antineoplastic Therapy.

**INTRODUCTION**

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues, it is not one disease but many disorders that share a profound growth dysregulation. Neoplasm is an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change. Cancer cells can spread to other parts of the body through the blood and lymph systems, this process is called metastasis.<sup>[1]</sup>

Cancer is the 2<sup>nd</sup> leading cause of death from disease in the US. Cancer kills one in two people in high-income countries and one in three people in low-to-middle-income countries<sup>[2]</sup> The continuing global demographic and epidemiologic transitions signal an ever-increasing cancer burden over the next decades, particularly in low and middle income countries (LMIC), with over 20 million new cancer cases expected annually as early as 2025.<sup>[3]</sup> 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012 worldwide.<sup>[4]</sup>

Traditional cytotoxic chemotherapy and the newer targeted systemic anti-cancer therapies are a part of a number of treatment modalities used to manage patients with malignant disease. Adjuvant chemotherapy and hormonal therapy can increase survival and prevent recurrent disease following surgical resection e.g. in ca breast, colorectal ca, ca lung etc.<sup>[5]</sup> Anticancer drugs are

useful in non-malignant diseases also- e.g. Autoimmune diseases e.g. RA (MTX, Cyclophosphamide), Crohn's disease (6-MP), Organ transplantation (MTX, Azathioprine), Sickle cell anaemia (Hydroxyurea). One of the major drawback of antineoplastic agents is, that they have lower therapeutic index and lower safety margins than doing so other drug classes.<sup>[6]</sup> Although chemotherapeutic complications may be associated with medication errors, and drugs can be administered via a variety of routes, this document focuses on the potential side effects associated with systemic anticancer therapies administered to adults, primarily via the intravenous or oral route and how can we make anticancer therapy more safe via their management and prevention strategies.

**Cancer Therapeutic Modalities (classical)<sup>[7]</sup>**

Surgery	} 1/3 of patients without metastasis respond to them
Radiation	
Chemotherapy	50% of patients need it to remove micrometastasis.

**Chemotherapy has five possible goals**

**Total remission** - to cure the patient completely. In some cases, chemotherapy alone can get rid of the cancer completely.

**Combination therapy** - chemotherapy can help other therapies, such as radiotherapy or surgery have more effective results.

**Delay/Prevent recurrence**

Chemotherapy, when used to prevent the return of cancer, is most often used after a tumour is removed surgically. Scientists at the Charite School of Medicine, Germany, found that the use of the drug gemcitabine for chemotherapy significantly delays the recurrence of cancer, compared to no chemotherapy.

**Slow down cancer progression**

Used mainly when the cancer is in its advanced stages and a cure is unlikely. Chemotherapy can slow down the advancement of cancer.

**To relieve symptoms**

Also more frequently used for patients with advanced cancer.

**General rules of chemotherapy**

**1. Combination** of several drugs with different mechanisms of action, different resistance mechanisms, different dose-limiting toxicities.

**2. Adjuvant therapy:** Additional cancer treatment given after the primary treatment to lower the risk that cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

**3. Neoadjuvant therapy:** Treatment given as a first step to shrink a tumour before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

**4. Aggressive high-dose chemotherapy**

**Dose-** limiting toxicity towards normal cells

**Cyclic regimens** - repeated administrations with appropriate intervals for regeneration of normal cells (e.g., bone marrow cells).

**5. Supportive therapy** - to reduce toxicity

- hematotoxicity – bone marrow transplantation, hematopoietic growth factors
- Specific antagonists:
  - Antifolate (methotrexate) –folate (leucovorin)
  - MESNA - donor of –SH groups, decreased urotoxicity of cyclophosphamide. Detoxifying agent.
  - dexrazoxane: chelates iron, reduced anthracycline cardiotoxicity
  - amifostine: reduces hematotoxicity, ototoxicity and neurotoxicity of alkylating agents

**Supportive therapy also includes**

- Antiemetics (5-HT<sub>3</sub>-antagonists)
- Antibiotic prophylaxis and therapy (febrile neutropenia)
- Prophylaxis of urate nephropathy (allopurinol)
- Enteral and parenteral nutrition
- Pain – analgesic drugs
- Psychological support.<sup>[8]</sup>

Thus in any way anticancer drugs are being used either prior or later in all the types of cancer and as these are the most cytotoxic agents thus high incidence of ADRs are there. Clinically useful antineoplastic agents exhibit selective toxicity to malignant cells. Many regenerating tissues possess high proliferative capacity rivaling malignant tissues and on exposure to chemotherapy, such tissues (bone marrow elements, gastrointestinal tract mucosa, hair follicles) endure the most of the toxic effects. The antineoplastic agents have the lowest therapeutic indices of any drug and as such they cause frequent and predictable multi system toxicity.<sup>[9]</sup> There are mainly acute toxicity in immediate post therapy periods which are usually reversible and long-term toxicity, which are delayed and irreversible. These increase the morbidity and mortality of treatment.<sup>[10]</sup> The incidence and severity of the toxicity of chemotherapy are greater in older patients with cancer than in younger patients and can complicate their treatment.<sup>[11]</sup> Thus during the last 15 years anticancer drug discovery has undergone a dramatic change to reduce the drug induced toxicities, which include, more cancer specific pathways, DNA repair defects, and identification of cell death, along with some steps like dose reduction, use of alternate drugs or their analogues, growth factors, and cytoprotective agents may protect from related toxicities.<sup>[9]</sup>

Common toxicities encountered are haematological, gastrointestinal, skin and hair follicle toxicity, nervous system toxicity, local toxicity, metabolic abnormalities, hepatic toxicity, urinary tract toxicity, cardiac toxicity, pulmonary toxicity, gonadal toxicity etc.<sup>[12]</sup> About the toxicities, drugs causing these and management of these toxicities are discussed in subsequent sections of this paper.

**Common side effects related to cancer chemotherapy, drugs causing them, how to prevent them and their management****A. Digestive System abnormalities**

Nausea, diarrhoea, dehydration and loss of appetite are some of the common symptoms associated with anticancer drugs, known as chemotherapy induced nausea vomiting (CINV) but may also be due to cancer itself.<sup>[4]</sup> Inadequate management of constipation, diarrhoea, nausea, or vomiting can affect patients in multiple ways, like decreased adherence to treatment regimen, anxiety and depression. Patients may become socially isolated and experience decreased function and abilities. Adequate management of gastrointestinal toxicities increases patient adherence to treatment regimens, decreases physiologic impairment, improves quality of life for patients and their caregivers, and prevents serious adverse events that lead to prolonged hospitalization and increased morbidity and mortality.<sup>[13]</sup> Table 1 has provided the grading of digestive abnormality.

**Table. 1: National Cancer Institute Common Terminology Criteria for Adverse Events: Gastrointestinal Toxicity.**<sup>[13]</sup>

Adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening or disabling)
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with activities of daily living; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per 24 hours over baseline; IV fluids indicated < 24 hours; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of 7 stools per 24 hours over baseline; incontinence; IV fluids 24 hours; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition indicated 24 hours	Life-threatening consequences
Vomiting	1 episode in 24 hours	2–5 episodes in 24 hours; IV fluids indicated < 24 hours	6 episodes in 24 hours; IV fluids or total parenteral nutrition indicated 24 hours	Life-threatening consequences

Grade 5 has been considered as death\*

### NAUSEA AND VOMITING

Nausea and vomiting can lead to dehydration and lack of nutrition. It is not a pathological process but rather a physiological process in which the body attempts to rid itself of toxic substances. Persistent writhing can result tears in the oesophagus. This is distressing enough to the patient to cause extreme physiologic and psychological

discomfort culminating in withdrawal from therapy (10) and for those who have had surgery, vomiting can be extra painful and could result in incision pulling apart. Commonly nausea begins 4 to 6 hours after treatment and lasts for 1 to 2 days. Table 2 has provided the list of anticancer drugs with potential of causing nausea and vomiting.

**Table. 2: Emetogenic risk of IV anticancer drugs.**<sup>[14-16]</sup>

Level 1 Frequency of emesis <10%	Level 2 Frequency of emesis 10-30%	Level 3 Frequency of emesis 30-60%	Level 4 Frequency of emesis 60-90%	Level 5 Frequency of emesis >90%
Bleomycin Hormone Vinorelbine Bevacizumab	Docetaxel Teniposide Thiopeta 5-Fluorouracil Topotecan Trastuzumab	Cyclophosphamide <750mg/m <sup>2</sup>	Carboplatin Oxaliplatin Doxorubicin Temozolomide	Carmustine>250mg/ m <sup>2</sup> , BCNU
Busulfan Melphalan	Etoposide	Doxorubicin 20-60mg/m <sup>2</sup>	Carmustine <250mg/m <sup>2</sup>	Cisplatin>59mg/m <sup>2</sup>
Hydroxyurea Mercaptopurine Chlorambucil	Gemcitabine	Epirubicin <90mg/m <sup>2</sup>	Cisplatin <50mg/m <sup>2</sup>	Cyclophosphamide >1500mg/m <sup>2</sup>
Vinblastine Vincristine	Methotrexate >50mg/m <sup>2</sup> <250mg/m <sup>2</sup>	Idarubicin Trabectedin Treoosulfan	Cyclophosphamide >750mg/m <sup>2</sup> < 1500mg/m <sup>2</sup>	Dacarbazine Streptozotocin Pentostatin Dacarbazine, DTIC

### Management

The goal of therapy is to prevent the three phases of nausea and vomiting. Anticipatory vomiting occurs before the treatment is administered, acute vomiting follows within the first 24 hours after the treatment and

that which occurs more than 24 hours after the treatment is delayed vomiting. Both antiemetic medications (listed in table3) and some alternative treatments such as acupuncture can help with nausea and vomiting related to chemotherapy.

**Table. 3: Antiemetics to treat CINV.**<sup>[14-20]</sup>

Class of antiemetics	Drug
Antihistamines	Cinnarizine
Benzodiazepines	Lorazepam
Anticholinergic drugs	Hyoscine
Dopamine inhibitors	Phenothiazines, Olanzapine-2.5–5 mg
Corticosteroids	Dexamethasone- Oral/i.v. 12 mg (highly emetogenic, with aprepitant), 20 mg without aprepitant; 8 mg (moderately emetogenic); 8 mg (high/moderate) days 2 and 3
5-HT <sub>3</sub> antagonists (5-HT <sub>3</sub> RAs)	Ondansetron- 16–24 mg orally and 8–12 mg (maximum, 32 mg) i.v. Dolasetron- 100 mg or 1.8 mg/kg i.v. and 100 mg Orally Granisetron- 1mg or 0.01 mg/kg i.v., and 2 mg orally Palonosetron i.v. 0.25 mg
Prokinetic drugs	Metoclopramide
NK1 receptor antagonists	Aprepitant Oral 125 mg on day 1, 80 mg on days 2 and 3
Cannabinoids	

**Coping with Nausea and Vomiting during Chemotherapy-** Medications can do a lot to ease nausea and vomiting that can occur during chemotherapy, but a few simple measures can help as well

- Eat small, frequent meals – Avoid eating too much, or going too long without eating
- Avoid drinking fluids during meals
- Remain upright after eating for half an hour
- Avoid odours that make you feel nauseated
- Avoid high fat and greasy foods before chemotherapy
- Wear clothes that are loose around abdomen
- Drink plenty of fluids
- Avoid smoking
- Avoid exercise right after eating

- Make surrounding environment and food as aesthetically pleasing as possible.<sup>[21]</sup>

### LOSS OF APPETITE AND WEIGHT LOSS

Loss of appetite and/or weight is pervasive and concerning among patients with cancer, particularly those with advanced-stage disease.<sup>[22]</sup> Cancer treatment also not only decreases appetite, but stomach may become full more quickly when eating.

### Management

Current pharmacological agents can be divided into three categories: orexigenic agents (appetite stimulants), anti-catabolic (anti-metabolic and anti-cytokine) agents, and anabolic agents (primarily hormonal), which are mentioned in table 4.

**Table. 4: Drugs to improve appetite.**<sup>[22-24]</sup>

Orexigenic agents	Anti-catabolic	Anabolic agents
megestrol acetate- 400mg/day	Eicosapentaenoic acid (EPA) (alpha-3 omega fatty acid)	Oxandrolone- 10mg twice daily for four months.
medroxyprogesterone	Thalidomide (TNF- $\alpha$ inhibitor)- 100mg per day	fluoxymesterone
Dexamethasone- 4mg/day	Pentoxifylline (inhibitor of TNF- $\alpha$ production)	
Cyproheptadine	hydrazine sulphate (inhibitor of phosphoenolpyruvate kinase)	

A few tips may help to boost up calories when a person doesn't feel particularly hungry

- Eat small portions frequently instead of 3 large meals daily
- Make surrounding environment pleasing. Dine with family and friends. Play music. Use lighting that feels comfortable
- Light exercise can sometimes stimulate appetite.
- Eat nutritious snacks that are high in calories and protein – Good choices include nuts, cheese and crackers, ice cream, peanut butter, and puddings
- Find foods that are comfortable to eat if you have mouth sores or taste changes
- Drink fluids between meals to avoid becoming full too

fast.

- Eat whenever feel hungry
- Try different foods – Sometimes a change in routine can make food more “interesting” and tempting.<sup>[21]</sup>

**Constipation or Diarrhoea:** Some chemotherapy drugs, pain relief medicines and anti-nausea drugs can cause constipation or diarrhoea.<sup>[25]</sup> After a bout of constipation or diarrhoea, eat a balanced diet with fresh fruits, vegetables, wholegrain bread and pasta.

**Constipation:** Factors and drugs which can cause constipation are listed in table 5.

**Table 5: Factors and drugs causing constipation.**<sup>[10]</sup>

Opioids	Hypercalcemia	Vinca alkaloids	Corticosteroids
Immobility	Hypokalemia	Decrease oral intake	Old age

**Management**

Chronic constipation is a problem in patients with cancer that is more easily prevented than treated.

- Increase fluid intake: warm or hot drink approximately half an hour before the time of patient's usual defecation.
- Increase fibre intake (e.g., psyllium 10 gm PO daily).
- laxatives and stimulants: magnesium sulphate 15 g PO daily, magnesium citrate 200 ml PO daily, lactulose 15 g PO daily, increase physical activity, if possible. Consider bowel regimen when constipating medications are prescribed (e.g., docusate 2–3 tablets per day, senna not to exceed 8 tablets a day). 15–60 ml PO daily, bisacodyl 5–20 mg PO at night or 10–20 mg rectally after a meal.<sup>[13]</sup>
- Don't use enemas or suppositories. They're not recommended for people having chemotherapy.
- If constipation stays for more than a couple of days, let the doctor or nurse know.<sup>[21]</sup>

A bowel regimen consists of initial mild stool softeners and bulk laxatives and then proceeding to stimulants or osmotic laxatives. Two of the most potent laxatives acceptable for long-term use are Lactulose & Sorbitol.<sup>[10]</sup>

**Diarrhoea:** The quantitative definition of diarrhoea is, stool weight of more than 200gm/day and the bowel movements are excessive in both frequency and liquid content. It has the potential to cause great morbidity. Among the many causes of diarrhoea in patients with cancer are chemotherapy, radiotherapy, cancer itself, medications, supplemental feedings, anxiety, and infection with bacteria like clostridium difficile.<sup>[25]</sup> See table 6 for drugs causing diarrhea.

**Table 6: Drugs causing diarrhoea.**<sup>[4]</sup>

Methotrexate	Paclitaxel	Floxuridine
Cytarabine	Irinotecan	Nitrosourea

**Management**

- Discontinue suspected medication. Start appropriate antibiotics. Begin supportive therapy.<sup>(10)</sup> Pharmacological management is given 12 to 24 hours later if an inadequate response or immediately if grade 3 or 4 diarrhoea begin. It includes agents like kaolin, pectin, loperamide, diphenoxylate hydrochloride, Octreotide.<sup>[26]</sup>
- Increase oral fluid intake (8–10 cups daily). Recommend water, electrolyte-replacement beverages,

**Table 8: Drugs causing oral toxicities.**<sup>[10]</sup>

Antimetabolites	Methotrexate, 5-Fluorouracil, Cytarabine, Irinotecan
Antitumor antibiotics	Doxorubicin, Dactinomycin, Mitomycin, Bleomycin
Plant alkaloids	Vincristine, Vinblastine, Etoposide
Others	Alkylating agents in high doses
Biologic agents	Interleukins
Antimetabolites	Methotrexate, 5-Fluorouracil, Cytarabine, Irinotecan

sports drinks, diluted fruit juices, and broth. Avoid caffeinated, carbonated, heavily sugared, and hyperosmotic beverages. Foods to avoid: alcohol, caffeine-containing products, carbonated and high-sugar beverages, fruit juices with pulp, high-fibre and high-fat foods, hot or heavily spiced foods, dairy products.

- Perineal care: Clean area using mild soap and water or wet wipes. Pat dry rather than rub dry; air dry when possible. Use skin barrier products, vitamin D ointment, diaper-rash cream, or other moisture-barrier products.
- Pharmacologic management for grade 1 diarrhoea that persists for more than 12–24 hours Antidiarrheal agent: loperamide 4 mg followed by 2 mg every four hours or after each unformed stool (maximum 16 mg per day). May take 4 mg every four hours at night to allow sleep.
- Stool cultures and sensitivity: rule out Clostridium difficile, ova, cysts, and parasites. Consider empiric antibiotic, (e.g., metronidazole). Consider tincture of opium 0.6 ml PO every four to six hours. Consider Sandostatin 100–150 mcg subcutaneously TID
- Correct electrolyte imbalance as needed.<sup>[13]</sup>

**B. Oral Toxicity:** Oral disease is common in subjects undergoing chemotherapy. Given their high rate of turnover, mucosal cells in the oral cavity are highly susceptible to the toxic effects of cancer treatment.<sup>[27]</sup> The mucosa can be secondarily infected if once ulcerated rendering a portal for systemic infection<sup>[28]</sup> results in stomatitis, dysphagia, oral ulceration, esophagitis, & proctitis with pain and bleeding. Mucositis is a common dose-limiting complication in patients receiving systemic anticancer chemotherapy, bone marrow transplantation, and local irradiation for tumours in the head and neck area. It appears clinically as erythematous or diffuse ulcerative lesions.<sup>[29-31]</sup> Table 7 depicts “World Health Organization Oral Mucositis grades” and in table 8, anticancer drugs causing oral toxicities are enlisted.

**Table 7: World Health Organization Oral Mucositis Scale adapted from.**<sup>[32,33]</sup>

Grade 1	Oral soreness, erythema
Grade 2	Ulcers, but able to eat solid food
Grade 3	Oral ulcers and able to take liquids only
Grade 4	Oral alimentation impossible

### Management

According to the National Institutes of Health consensus conference statement<sup>[34]</sup>, all cancer patients should have an oral examination before initiation of cancer therapy and treatment of pre-existing or concomitant oral disease

is essential in minimizing oral complications. Once mucositis has occurred, treatment consists of measures to palliate symptoms.<sup>[35]</sup> Regimens for oral care and oral toxicity treatment is mentioned in table 9.

**Table. 9: Agents for Oral Care.**

<b>Cleansing agents</b>	Normal saline, hydrogen peroxide, sodium bicarbonate, Chlorhexidine
<b>Lubricating agents</b>	Saliva substitutes, water or oil base lubricants
<b>Analgesic agents</b>	Healing & coating agents Sucralfate, Vitamine E, Antacids, Allopurinol Topical anaesthetics Lidocaine, Benzocaine, Diclomine hydrochloride Systemic analgesics NSAID, Narcotic analgesics

### Preventive strategies for oral toxicities

- Use a soft tooth brush to clean teeth twice a day.
- Commercial mouthwashes containing alcohol are prohibited, as they may dry out or irritate the mouth. Instead, try homemade mouthwash (1 tsp bicarbonate of soda or salt in a glass of warm water) at least four times a day. This helps keep the mouth clean, while the salt mouthwash helps heal mouth sores.
- Sip fluids, especially water, and eat moist foods such as casseroles or soups in case of a dry mouth. Moisten foods with butter and sauces.
- Try sucking on ice in case of intravenous chemotherapy to reduce mouth ulcers.
- Nourishing drinks such as milkshakes, smoothies and supplements add extra energy to diet and feel soothing.
- Avoid very hot foods, and spicy, acidic or coarse foods, (e.g. nuts or grains), as these can aggravate mouth sores.
- Don't smoke or drink alcohol, as this irritates tissue in the mouth
- Eat a good diet with a variety of foods. Some vitamin deficiencies can make symptoms worse, and a good diet may help body to fight off infection
- Avoid foods that are spicy, salty, and hard (like toasts) or foods with citrus acid and tomato juice. Pineapple and strawberries are often tolerated well than other fruits, and grape or apple juice may cause less discomfort than citrus and tomato juices.
- Avoid foods with extreme temperatures
- Drink plenty of water
- Good food choices can include — mashed potatoes, cooked cereals, applesauce, cottage cheese, pudding, yoghurt, smoothies (without citrus,) soups, Jello, baby food, or food pureed in the blender.<sup>[21]</sup>

### C. Fatigue

Fatigue is a subjective experience. It is a matter of concern due to its high prevalence and negative effects on quality of life besides treatment factors, fatigue is often due to the tumor itself. Sufferers may exhibit symptoms that are physical (physical weakness or tiredness), emotional (depression), motivational (lack of initiative or motivation), cognitive (impairment of

cognitive function), and social (reduced ability to sustain social relationships). (36) Of all the chemotherapy side effects, fatigue is one of the most distressing. Unlike ordinary tiredness, chemotherapy-related fatigue is frequently described as tiredness that does not resolve with rest, “whole body” tiredness or a feeling in which even the most mundane activities require effort. Fatigue may begin shortly into treatment and can persist for up to a year, and maybe more, following completion. The first step toward coping with cancer-related fatigue is to understand that it is normal and common.<sup>[10]</sup>

### Management

- **Eat Regularly-** Eating regular meals is very helpful when it comes to maintaining baseline energy level. Avoid becoming overly hungry or eating in excess. In addition, emphasizing complex carbohydrates and protein-rich foods over sugary treats and fats can prevent some of the highs and lows in energy level.
- **Get Enough Sleep-** Try to get at least 8 hours of sleep each night, and nap during the day if needed. On the other hand, too much rest can also make tired.
- **Keep surrounding comfortable-** Setting the thermostat at a comfortable temperature – not too hot, not too cold – can help maintaining energy level as well. Avoid hot showers, long hot baths, or activities where one can become chilled.
- **Moderate Exercise-** choose an activity that is enjoyable and an amount of time that feels comfortable.
- **Pacing-** With cancer fatigue, slow and steady wins the race. Rushing tends to tire out more quickly and can add to anxiety level as well. Many cancer survivors find that taking short, frequent rest periods during the day instead of one long period of rest is helpful.
- **Avoid Alcohol and Caffeine-** Both alcohol and caffeine can contribute to tiredness during cancer treatment. A cup of coffee in the morning probably won't hurt, but using caffeine to stay awake can backfire and leave feeling more tired.

• **Manage Stress-** Find ways to relieve stress that find enjoyable. Meditation, yoga, or prayer are helpful for some people; others find reading, listening to music, or a walk in a park to be calming. Visualization is being taught in many cancer centres, both as a way to cope with the symptoms of cancer and as a method of moving past the inevitable stress of cancer treatment.<sup>[21]</sup>

**D. Haematological Toxicity:** Peripheral cytopenia from bone marrow suppression is a frequent dose limiting side effect of chemotherapy and can manifest as acute and chronic marrow damage. Drug-induced hematologic disorders can affect any cell line, including white blood cells (WBCs), red blood cells (RBCs), and platelets. When a drug causes decreases in all three cell lines

accompanied by a hypoplastic bone marrow, the result is drug-induced aplastic anaemia. The decrease in WBC count alone by a medication is drug-induced agranulocytosis. Drugs can affect RBCs by causing a number of different anaemias, including drug-induced immune hemolytic anaemia, drug-induced oxidative hemolytic anaemia, or drug-induced megaloblastic anaemia. A drug-induced decrease in platelet count is drug-induced thrombocytopenia.<sup>[37]</sup> Chemotherapy may result in the destruction of activity of proliferating haematopoietic precursor cells, leading to deprivation of formed elements, and incidence of life threatening haemorrhage and infection.<sup>[38]</sup> Drugs causing bone marrow depression are mentioned in table 10.

**Table. 10: Drugs causing bone marrow depression.**

Carboplatin	Dactinomycin	Vinblastine	Doxorubicin
Chlorambucil	Procarbazine	Oxaliplatin	Hydroxyurea
Ifosamide	Fludarabine	Transtuzumab	Paclitaxel
Vinorelbine	Mitoxantrone	Rituximab	Daunorubicin
Cytarabine	Topotecan FU	Irinotecan	Methotrexate
Cyclophosphamide	Mitomycin	Idarubicin	Gemcitabine
Oxaliplatin	Mustine	Melphalan	

#### ANAEMIA

The aetiology of anaemia in the patient with cancer is multifactorial and includes blood loss, absent nutritional stores, marrow infiltration and direct effect of cytotoxic drugs. Anticancer drugs causing anaemia are enlisted in table 11.

**Table. 11: Anticancer drugs causing anaemia.**

Cisplatin	Altretamine	Topotecan
Docetaxel	Cytarabine	Paclitaxel

#### Aplastic anemia

Aplastic anaemia is a rare, serious disease of unclear aetiology. Acquired aplastic anaemia is characterized by pancytopenia (anaemia, neutropenia, and thrombocytopenia) with a hypocellular bone marrow and no gross evidence of increased peripheral blood cell destruction.<sup>[39]</sup>

#### Management

• **Transfusions-** The fastest way to increase red blood cells is with a blood transfusion. Side effects can include a fever and chills, and the small risk of having a blood transfusion reaction or contracting an infectious disease such as hepatitis.

• **Iron Supplements-** Oral or IV iron supplements might be recommended. Iron taken orally is easiest but can cause stomach discomfort. Common side effects of intravenous iron are a transient feeling of flushing, a metallic taste, headaches, and joint or muscle aches a few days after treatment. Occasionally, iron injections can cause allergic reactions that can be serious.

• **Medications to stimulate the formation of red blood cells-** There is currently a lot of controversy about this treatment. These medications include Epoetin alfa (Epoen, Procrit) and Darbepoetin alfa (Aranesp).<sup>[21]</sup>

#### Coping With Anaemia during Chemotherapy

The best way to cope with anaemia is to take it easier than usual until the body is able to catch up and make more red blood cells. The good news is that anaemia is one cause of fatigue that is very treatable, and it will usually begin to improve a few weeks after completing chemotherapy.

- Get an adequate amount of sleep and nap when needed
- Stand up slowly, especially when sitting or lying down for an extended period of time
- Drink plenty of water
- Avoid caffeine, tobacco, and alcohol

#### Agranulocytopenia

Agranulocytosis is defined as a reduction in the number of mature myeloid cells in the blood (granulocytes and immature granulocytes [bands]) to a total count of 500 cells/mm<sup>3</sup> ( $0.5 \times 10^9$  /L) or less. Symptoms of agranulocytosis arise from the increased infection risk associated with the lack of WBCs and include a sore throat, fever, malaise, weakness, and chills. Symptoms may appear either immediately or insidiously, depending on the time course of neutropenia development.<sup>[37]</sup> Neutropenia is absolute neutrophil count < 500cell/mm<sup>3</sup> and count <1000cell/mm<sup>3</sup> with a predicted decrease to 500cell/mm.<sup>[40]</sup>

#### Management

- Preventative Antibiotics- Sometimes antibiotics are used preventatively before any signs of infection.
- Medications- growth factors may be used to stimulate the production of neutrophils preventively or as a treatment for a low neutrophil count.

#### These include

- Filgrastim, G-CSF (Neupogen)
- Pegfilgrastim (Neulasta)
- Sargramostim, GM-CSF (Leukine)

#### Preventive strategies

- Practice careful hand washing– This is the **most important** thing to do to lower risk
- Use liquid soap instead of bar soap
- Stay away from people with infections
- Avoid large crowds, for example, shopping malls and movie theatres
- Avoid children (and adults) that have recently received vaccinations with live viruses, such as the chickenpox vaccine
- Skip any immunizations (for example the flu shot or pneumonia shot) until discussed these with oncologist
- Avoid any dental work
- Avoid raw eggs and undercooked meat, fish, or seafood. Use Safe Cooking Practices
- Pets can be a source of infection when white blood cell count is low – Have someone else change the litter box, clean the bird cage, or change the fish tank. Avoid handling reptiles. This is the real reason to step back and allow others to help – take advantage of it.
- Ask physician before using medications such as acetaminophen (Tylenol). These can mask a fever
- Women should avoid tampons, and use sanitary napkins
- Use an electric shaver
- Avoid cutting your cuticles. It is best to avoid manicures and pedicures as well until the completion of chemotherapy.<sup>[21]</sup>

#### Thrombocytopenia

Thrombocytopenia creates a number of problems in the care of a cancer patient. At platelet counts < 100,000/ $\mu$ L, chemotherapy and radiation therapy are administered with caution for fear of worsening the thrombocytopenia and increasing the risk of bleeding. At platelet counts < 50,000/ $\mu$ L, surgical procedures are often complicated by bleeding. At platelet counts < 10,000/ $\mu$ L, spontaneous bleeding is increased.<sup>[41]</sup> Table 12 shows drugs causing thrombocytopenia.

**Table. 12: Drugs causing thrombocytopenia.**

Dacarbazine	Lomustine	Carboplatin
5-fluorouracil	Mitomycin	Thiotepa

#### Management

- Reduce chemotherapy dose and/or frequency or alter the chemotherapy regimen, especially if chemotherapy is not standard or not of curative intent.<sup>[42]</sup>

• Platelet transfusions - Prophylactic platelet transfusions are indicated if bleeding occurs or if platelet counts are < 10,000/ $\mu$ L (or with platelet counts < 20,000/ $\mu$ L if the patient is febrile).<sup>[43,44]</sup> The most common side effect is a temporary fever. Rare side effects can include transfusion reactions, or contract an infection such as hepatitis

• Medications that stimulate the formation of platelets - Medications are sometimes used to stimulate the bone marrow to make more platelets.

○ Thrombopoietin receptor agonists-Those who cannot be supported by platelet transfusions romiplostim at 2–3  $\mu$ g/kg weekly, or 50–75 mg of eltrombopag daily to maintain platelet counts over 100,000/ $\mu$ L, in order to allow continuation of chemotherapy (Figure 6). Thrombopoietin receptor agonists would be started only when the patient's platelet count had failed to recover to levels > 100,000/ $\mu$ L before the next scheduled chemotherapy.<sup>[42]</sup> Its most common side effect is fluid retention (swelling).

• Antifibrinolytic agents such as epsilon-aminocaproic acid or tranexamic acid have been used in some thrombocytopenic cancer patients to decrease the bleeding risk when platelet transfusions did not work.<sup>[45]</sup> Total daily doses of 2–24 g (mean, 6 g) of epsilon-aminocaproic acid given in 3 or 4 divided doses have been used.<sup>[46]</sup> Tranexamic acid doses of 4–6 g/d given as 3 or 4 divided doses have also been studied.<sup>[47]</sup>

• The use of vincristine, rituximab, prednisone, IVIG, splenectomy, or anti-D immunoglobulin is rarely justified in patients with chemotherapy-induced thrombocytopenia, despite their widespread use and efficacy in ITP.

• The use of IL-11 is rarely justified, given its significant side effects. Recombinant IL-11 (oprelvekin) has been shown to reduce the need for platelet transfusions from 96% to 70% of patients who had been transfused with platelets in a prior cycle and who then received additional chemotherapy.<sup>[48]</sup>

#### Preventive strategies

If patient is at risk for thrombocytopenia try to

- Avoid aspirin and anti-inflammatory medications such as ibuprofen. Ask your doctor about any over-the-counter or herbal medications you take, since some of these can increase bleeding
- Avoid alcohol
- Use a gentle toothbrush. Many oncologists recommend that you avoid using dental floss as well, but this has not been proven to help
- Use an electric razor
- Blow nose gently
- Avoid constipation.
- Avoid situations where you could be injured or otherwise hurt. Avoid contact sports.<sup>[21]</sup>

#### E. Toxicity Of Skin And Related Structures

Anticancer chemotherapy induced side effects affects nearly every structure of the skin especially skin adnexes such as hair cause alopecia.<sup>[49]</sup> The frequency of mucocutaneous complications in cancer chemotherapy is

a reflection of the increased proliferative state of tissues, such as the mucous membranes, skin, hair, and nails, which renders them particularly susceptible to the actions of chemotherapeutic drugs.<sup>[50]</sup> See table 13.

**Table. 13: Drugs causing various skin changes.**<sup>[50]</sup>

<b>Nail Changes</b>	<b>Erythema multiforme</b>	<b>Pigmentation</b>	<b>Urticarial</b>
Cyclophosphamide	5-Fluorouracil	6-Mercaptopurine	Cytosine arabinoside
Ifosfamide	Bleomycin	Methotrexate	Doxorubicin
Doxorubicin	Vinblastine	Bleomycin	Daunorubicin
Daunorubicin	Doxorubicin	Cyclophosphamide	Carboplatin
	Daunorubicin	Ifosfamide	Asparaginase
<b>Skin peeling</b>	<b>Hand foot reaction</b>	<b>Photosensitivity</b>	
Cytosine arabinoside	Bleomycin	Methotrexate	
	Hydroxyurea	Vinblastine	

#### Preventive measures<sup>[51]</sup>

- Skin care and hygiene
- Thick alcohol free emollient to prevent xerosis
- Topical antibiotics if pustules are developed e.g: tetracycline
- Topical steroids are controversial with secondary side effects
- Topical retinoid for follicular eruptions but avoided for dryness and peeling
- Use of sunscreen of at least SPF 15 preferably containing zinc oxide or titanium oxide

#### Alopecia

Although dermatological complications are rarely fatal, it is important to recognize potential reactions in the management of the cancer patient, as they may result in significant morbidity, cosmetic disfigurement, and psychological distress. Hair loss is usually more of a nuisance than a symptom, but it can be distressing nonetheless. According to research, hair loss is one of the most feared side effects of chemotherapy. Some medications are more likely to cause hair loss than others, and hair loss can range from a little thinning to total baldness. It helps to be aware (and frequently comes as a surprise) that all hair can be affected, and it is not uncommon to lose eyebrow hair, facial hair, and even pubic hair. Hair loss usually begins a week or so after the start of chemotherapy and begins to grow back 6 to 8 weeks after completing therapy.<sup>[10]</sup> See table 14.

**Table. 14: Drugs causing hair follicle toxicity.**<sup>[10]</sup>

Doxorubicin	Paclitaxel	Vincristine
Daunorubicine	Ifosfamide	Methotrexate
Cyclophosphamide	Etoposide	Cisplatin

#### Management

Hair usually begins to grow when treatment that induces alopecia is complete. Doctors may consider referral to the patient's haematology/oncology team if hair does not begin to return within 6 months following the completion of treatment (5), in very few cases cessation of therapy is

sometimes required due to the severity of adverse reactions.<sup>[52]</sup>

- Imuvert-a membrane vesicle ribosome preparation from a bacterium either partially or completely reverse the alopecia caused by the chemotherapeutic agents.<sup>[53]</sup>

- Scalp cooling (not done in case of brain metastasis).(5)

#### Preventive measures

Both during chemotherapy and as hair begins to grow again after treatment, caring for hair may delay hair loss and facilitate regrowth. Short hair looks fuller, places less weight on the roots (which may help hair last longer), and may ease the transition to total hair loss. It is can also be helpful to shop for wigs or other head covers before you lose your hair. Other tips for caring for hair before and after treatment include

- Use a mild shampoo, such as baby shampoo, to wash hair
- Brush hair gently with a soft baby brush or wide-toothed comb
- Try to limit washing hair to a few times per week
- Avoid ponytails, braids, and hair accessories that pull hair
- Limit the use of hair dryers, and use a low heat setting when need to use a dryer
- Avoid hair dyes and permanents
- Use a satin pillowcase
- Protect scalp from the sun with coverings and/or sunscreen.<sup>[21]</sup>

#### F. Nervous System Toxicity

The incidence of neurotoxicity associated with chemotherapy is increasing because of greater use of high dose chemotherapy and newer drugs causing neurotoxicity used in combination weakening the barrier found with the brain, with symptoms of numbness, tingling, or burning in the hands and feet.<sup>[54]</sup> Anticancer chemotherapy can permanently damage both the central and the peripheral nervous systems, but the mechanism(s) of this toxicity is largely unknown. In most cases, cancer induced peripheral neuropathy

(CIPN) ensuing after conventional treatments consists of dose-dependent, predominantly sensory, length dependent neuropathies/neuronopathies. More rarely, motor, autonomic, or cranial nerve involvement also can be observed.<sup>[55]</sup> Patients with CIPN can experience

negative (i.e., impairment in touch, pin and vibration perception, sensory ataxia with imbalance and falls) as well as positive (i.e., paresthesias/ dysesthesias, neuropathic pain) symptoms.<sup>[56-59]</sup> Drugs causing neurotoxicity are listed in table 15.

**Table. 15: Neurotoxicity associated with cytotoxic drugs.**<sup>[10,55,60]</sup>

<b>Acute myelopathy</b>	<b>Cerebellar syndrome</b>	<b>Autonomic neuropathy</b>
Intrathecal cytarabine	Cytarabine	Vincristine Cisplatin
Intrathecal methotrexate	Procarbazine	Paclitaxel
Intrathecal thiotepa	5-Fluorouracil	Procarbazine
	MTX	
	Cyclosporine	
	Platinum derivates	
<b>Encephalopathy</b>	<b>Cranial nerve toxicity</b>	<b>Peripheral Neuropathy</b>
Carmustine	Vindesine	Vincristine
Cytarabine	Carmustine	Paclitaxel
Procarbazine	Ifosamide	Vindesine
5-Fluorouracil	Vincristine	Procarbazine
Ifosamide	Cisplatin	Vinblastine
Cisplatin	Vinblastine	Carboplatin
Methotrexate (MTX) 5-fluorouracil (5-FU)		Ipilimumab, Regorafenib(O)
Paclitaxel	<b>Seizures</b>	<b>Aseptic meningitis</b>
Cytosinarabinoside (Ara-C)	MTX, , asparaginase	MTX
Interferon- $\alpha$ Interleukin-2	etoposide, dacarbazine,	Ara-C (intrathecally)
Etoposide	Cis-platinum, amsacrin Busulfan	
Steroids High dose with stem cell transplantation	Vincristine, BCNU	

### Management

The only effective therapy is discontinuation of the causative chemotherapeutic agent. Medications may be used patient is experiencing pain. For mild symptoms, pain medications such as Tylenol (acetaminophen) or Advil (ibuprofen) may provide adequate relief. Other treatments that are sometimes used include:

- Vitamins such as B-complex supplements
- Antidepressants such as nortriptyline or amitriptyline
- Antiepileptic drugs (seizure medications) such as gabapentin or pregabalin
- Narcotic pain medications for severe pain

Complementary therapies may also help relieve the pain from neuropathy. Some treatments that have been looked at with chemotherapy-induced peripheral neuropathy include

- Massage therapy
- Physical therapy and/or occupational therapy
- TENS (transcutaneous electrical nerve stimulation)
- Acupuncture
- Biofeedback
- Guided imagery and relaxation.<sup>[21]</sup>

### Preventive strategies

- Protecting hands and feet from extremes in heat and cold — wearing good, comfortable shoes and using gloves when out in the cold or when cleaning or

gardening

- Checking hands and feet daily for any sores that might otherwise not feel due to decreased sensation
- Practicing caution when handling objects (such as cooking) that able to grip well or not
- "Fall proofing" home environment, being careful to remove objects that might cause injury
- Avoiding prolonged standing.
- Avoiding alcohol.<sup>[21]</sup>

### G. Hyper Sensitivity & Anaphylaxis

All chemotherapeutic agents can cause anaphylaxis. The drug most commonly associated with anaphylaxis is L-asparaginase. Factors that increase the incidence and degree of hypersensitivity include the route of entry, amount of antigen introduced, the rate of antigen absorption, specific chemotherapeutic agent, and prior exposure to the drug. Mostly type I reactions are observed frequently in clinical practice.<sup>[61]</sup> See table 16 for drugs causing hypersensitivity.

**Table. 16: Drugs causing hypersensitivity.**

Carboplatin	Doxorubicin	Cyclophosphamide
Paclitaxel	Docetaxel	Cisplatin
Cytarabine	L-asparaginase	Ifosfamide

### Management

- Graded scaling for anaphylactic symptoms must be done.
- Drugs, which cause these reactions, should be administered under supervision.
- Once a reaction occurs immediately stops the infusion.
- Assess airway, breathing and circulation. Closely monitor the patient's vital signs.
- Administer oxygen as needed and IV fluids.<sup>[21]</sup> See table 17 for management of hypersensitivity

**Table. 17: Management of chemotherapy induced hypersensitivity.**<sup>[62]</sup>

Severity of Reaction	Symptoms & Signs	Initial Management	Re-challenge
Mild	Can include: <ul style="list-style-type: none"> <li>• Erythema/itch</li> </ul>	<ul style="list-style-type: none"> <li>• Chlorphenamine 10mg intravenous bolus over 1 min</li> <li>• Hydrocortisone 200mg slow intravenous bolus</li> </ul>	When signs and symptoms subside restart infusion at a lower infusion rate
Moderate	As above and: <ul style="list-style-type: none"> <li>• Tachycardia</li> <li>• Throat/chest tightness/pain</li> <li>• Abdominal/back pain</li> </ul>	<ul style="list-style-type: none"> <li>• 100% O<sub>2</sub></li> <li>• Chlorphenamine 10 mg intravenous bolus over 1 min</li> <li>• Hydrocortisone 200mg slow intravenous bolus</li> <li>• Establish intravenous infusion of sodium chloride 0.9% until Medical Officer arrives</li> </ul>	Do not re-challenge on that day Monitor patient for 1 hour Reassess medically & allow home if stable Warn patient of risk of relapse when drugs wear off Consider oral Chlorphenamine 4mg PRN for 24-48 hours If re-challenging, do so at a reduced rate after consulting the SPC
Severe	As above and : <ul style="list-style-type: none"> <li>• Hypoxia</li> <li>• Wheezing</li> <li>• Hypotension</li> <li>• Persisting and escalating symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• 100% Oxygen</li> <li>• 500micrograms Adrenaline (Epinephrine) 0.5ml 1:1000 by deep intra-muscular injection – can be repeated every 5 mins in absence of clinical improvement</li> <li>• Secure airway</li> <li>• If hypotensive, lie flat and raise legs or if patient vomiting lie on their side</li> <li>• Establish intravenous infusion of sodium chloride 0.9% until Medical Officer arrives</li> <li>• Chlorphenamine 10mg intravenous bolus over 1 min</li> <li>• Hydrocortisone 200mg slow intravenous bolus</li> </ul>	<b>Consultant makes the decision whether to re-challenge or not</b> Admit for observation Assisted ventilation and ICU may be necessary Do not re-challenge on that day and if re-challenging, do so at a reduced rate after consulting the SPC

### H. Metabolic Abnormalities

A rapid destruction of tumour cells by anticancer drugs results in increased metabolism of nucleic acid, released from these cells. This increases the uric acid level precipitate nephrotoxicity. Massive tumour lysis releases intracellular potassium and phosphate causing severe hyperkalemia and hyperphosphatemia leading to hypocalcaemia and is called tumour lysis syndrome.<sup>[63]</sup>

**Management:** Patient who has tumour lysis syndrome must have adequate hydration with half normal saline solution.<sup>[64]</sup>

### I. Hepatic Toxicity

Virtually most subjects undergoing chemotherapy have exposure to hepatotoxins including medication and

alcohol. Chemotherapeutic agents that cause hepatotoxicity produce a predictable pattern of injury where the mechanism is direct or idiosyncratic.<sup>[65]</sup> Chemotherapy-induced hepatic injuries (CIHI) are divided into two main groups:(i) chemotherapy-associated fatty liver diseases, the spectrum of which includes chemotherapy-associated simple steatosis(CASS) and chemotherapy-associated steatohepatitis (CASH) and (ii) sinusoidal injuries, including sinusoidal dilation and congestion, sinusoidal obstruction syndrome (SOS), hemorrhagic centrilobular necrosis (HCN) and nodular regenerative hyperplasia (NRH).<sup>[66]</sup> It has been seen that cytotoxic chemotherapy impairs phagocytic activity of kupffer cells<sup>[67]</sup> reduced synthesis of humoral factors for host cells defense mechanism may also be critical for developing infections. See drugs causing hepatotoxicity in table 18.

**Table. 18: Drugs causing hepatotoxicity.**<sup>[68]</sup>

Hepatitis Disease	Cholestasis	Biliary Stricture	Steatosis	Nodular Hyperplasia Fibrosis	Veno-Occlusive Disease
Asparaginase	Azathioprine	Cytarabine	Asparaginase	Methotrexate	Cyclophosphamide
Carmustine	Erlotinib	Floxuridine	Cytarabine	Oxaliplatin	Oxaliplatin
Floxuridine	Floxuridine		Fluorouracil	Thioguanine	Thioguanine
Imatinib	Interleukin		Irinotecan		Mitomycin
Interferon	Topotecan		Oxaliplatin		Melphalan
Methotrexate	Sorafenib				Fluorouracil
Pazopanib	Paclitaxel				Doxorubicin

### Management

- Reduction in dose or intermittent therapy is done other than supportive management.
- Defibrotide can reverse the Veno-occlusive disease of the liver caused by all drugs at high doses except cisplatin.

### J. Renal Toxicity

Kidneys are vulnerable to the development of drug toxicity due to their role in the metabolism and excretion of toxic agents.<sup>[69]</sup> Renal tubules and the proximal segment, in particular, have significant capacity for uptake of drugs via endocytosis or transporter proteins,

contact of the bladder wall with toxic metabolites of cyclophosphamide like acrolein produces mucosal erythema, inflammation, ulceration, necrosis and a reduced bladder capacity.<sup>[70]</sup> Major risk factors for renal toxicity in patients with cancer include nephrotoxic chemotherapy drugs, age, nutritional status, use of nephrotoxic drugs, pre-existing renal dysfunction.<sup>[71]</sup> of these impaired renal function is the most significant risk factor. Acute renal failure and haemolytic uremic syndrome are serious and fatal complications. Anticancer drugs involved in causing nephrotoxicity are mentioned in table 19.

**Table. 19: Drugs causing Nephrotoxicity.**<sup>[69]</sup>

Drugs with tubular toxicity	Drugs with glomerular toxicity	Drugs causing electrolyte abnormalities
Cisplatin	Gemcitabine	EGFR antibody
Ifosfamide	Mitomycin	Cetuximab
Methotrexate	Bevacizumab	Panitumumab
Pemetrexed	Sunitinib	Imatinib
Ipilimumab	Axitinib	
	Pazopanib	

### Management

- The Acrolein conjugator, MESNA (2-mercaptoethanesulphonatesodium) acts by binding to acrolein and result in a non-toxic Thioether. Use of MESNA and hydration significantly reduce the incidence of bladder toxicity with Ifosfamide or high dose Cyclophosphamide.
- Acetylcysteine is a sulfhydryl compound used for the same purpose.

- Depending on the degree of toxicity, bladder irrigation, and fulguration and in rare instances cystectomy may be warranted.
- Renoprotective agents should be used, as mentioned in table 20.

**Table. 20: Renoprotective agents.**<sup>[72]</sup>

Mechanism of action	Molecular target
Antioxidants	N-acetylcysteine, Glutathione, Catalase, capsaicin, hyperbaric oxygen, quercetin, gum arabic, rebamipide
Suppresses inflammation	TNF-a, IL-10
Others	L-Arginine, Rosiglitazone, fibrates, Amifostine, Procaine hydrochloride

### K. Pulmonary Toxicity

Pulmonary toxicity is uncommon with most chemotherapy agents and typically consists of parenchymal lung injury ("pneumonitis" or interstitial lung disease), drugs can damage directly or indirectly, lung tissue both of endothelial and epithelial cells.<sup>[73]</sup>

This lung injury can be severe, sometimes resulting in progressive respiratory failure and death, as illustrated by Yoh *et al.*<sup>[74]</sup> Clinical presentations of pulmonary toxicity are acute pneumonitis, pulmonary fibrosis, hypersensitivity pneumonitis, non-cardiogenic pulmonary oedema, pleural manifestations, airway

diseases, pulmonary vascular abnormalities, mediastinal changes, and neuromuscular effects.<sup>[75,76,77]</sup> Many patients will exhibit symptoms and histological findings

of more than one type of toxicity. Drugs causing pulmonary toxicity are mentioned in table 21.

**Table. 21: Drugs causing pulmonary toxicity.**<sup>[78]</sup>

Acute pneumonitis	Pulmonary fibrosis	Hypersensitivity pneumonitis	Non-cardiogenic pulmonary oedema
Mitomycin	Bleomycin	Methotrexate	Mitomycin
Carmustine	Cyclophosphamide	Bleomycin	Cytarabine
Procarbazine	Busulfan	Azathioprine	Methotrexate
Methotrexate		Procarbazine	Cyclophosphamide
Vinca alkaloids			Cytosine arabinoside
Bleomycin			

### Management

- During drug therapy, monitoring of symptoms and signs, PFTs and chest radiographs can aid in detecting problems early, and the causative agent can be withdrawn.<sup>[79]</sup>
- A chronic cough, dyspnea or change in exercise should be further evaluated with chest radiography and PFTs.
- Recent clinical studies have shown a reduction in pneumonitis using amifostine in chemoradiation treatments for lung cancer.<sup>[80,81]</sup>
- Smoking cessation

### Preventative strategies

- A study of inhaled fluticasone propionate, however, demonstrated some potential benefit with a reduction of acute pneumonitis in patients treated for breast cancer.<sup>[82]</sup>

### L. Cardiac Toxicity

Cardiotoxicity occurs during therapy with several cytotoxic drugs and may be the dose limiting factor in cancer treatment and hence tumor response. Cardiotoxicity includes a wide range of cardiac effects from small changes in blood pressure and arrhythmias to cardiomyopathy. In literature different mechanisms of chemotherapy induced cardiotoxicity are postulated including cellular damage due to the formation of free oxygen radicals and the induction of immunogenic reactions with the presence of antigen presenting cells in the heart.<sup>[83]</sup> Myocardial ischemia, pericarditis, arrhythmia, ECG changes and angina occur much less frequently.<sup>[84]</sup> Drugs associated with cardiotoxicity are mentioned in table 22.

**Table. 22: Anticancer drugs associated with cardiotoxicity.**<sup>[85]</sup>

Left ventricular dysfunction	Myocardial Ischemia	Hypertension	QT Prolongation	Thromboembolism
Anthracyclines – Epirubicin, Doxorubicin (Adriamycin)	Capecitabine	Bevacizumab	Vorinostat	Cisplatin
Alkylating agents Cyclophosphamide, Ifosfamide	Fluorouracil	Sorafenib	Arsenic trioxide	Lenalidomide
Clofarabine	Paclitaxel	Sunitinib	Dasatinib	Thalidomide
Docetaxel	Docetaxel			Vorinostat
Bevacizumab	Bevacizumab	<b>Bradycardia</b>	Lapatinib	Erlotinib
Bortezomib	Erlotinib	Thalidomide	Nilotinib	
Dasatinib	Sorafenib	Paclitaxel		
Imatinib mesylate				

### Management

- Minimize the patient's lifetime cumulative dose of anthracyclins.<sup>[86]</sup>
- Risk-factor reduction by controlling HTN, diabetes, and hyperlipidemia, with the goal of preventing remodelling
- Use of cardioprotection iron chelator, dexrazoxane represents the primary prevention approach.<sup>[87]</sup>
- All patients should be on a combination of an angiotensin-converting enzyme (ACE) inhibitors or an angiotensin II receptor blocker and a beta-blocker unless contraindicated.
- Patients with end-stage HF with refractory symptoms at rest despite maximal medical therapy and without

evidence of cancer recurrence could be considered for synchronized pacing, ventricular assist device, or cardiac transplantation.<sup>[88]</sup>

- Suspected ACS (Acute coronary syndrome) should be managed according to the guidelines established by American College of Cardiology and American Heart Association<sup>[89,90]</sup>, like coronary intervention, antiplatelet and anticoagulant therapy.
- For Hypertension, medications should be initiated in concordance with JNC guidelines.<sup>[91]</sup>
- Patients who develop VTE (venous thromboembolism) should be treated in accordance with established guidelines put forth by the American College of Chest

Physicians. In general, for patients with VTE and cancer, the guidelines recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy, followed by anticoagulant therapy with warfarin or LMWH indefinitely or until the cancer is resolved.<sup>[92]</sup>

- Overdrive trans venous pacing may be used to shorten the QTc. Pacing is highly effective in preventing recurrence and may be useful in cases refractory to magnesium or when torsade de pointes is precipitated by bradycardia. Isoproterenol titrated to a heart rate 90 beats/min is another option in patients, and it is useful when temporary pacing is unavailable or while preparing for transvenous catheter insertion maintain serum potassium levels in the high-normal range, and discontinue any QT prolonging medications and drugs interfering with patients' metabolism.<sup>[93]</sup>

### Miscellaneous

There are many more other toxicities countered to antineoplastic therapy like ocular, Secondary neoplasm, Infertility, Teratogenicity, sexual impotence etc.

### CONCLUSION

Although chemotherapy is quite toxic and drugs are of very low therapeutic index but looking at benefit outweigh the risk, these drugs have to be given in cancer management. These side effects and complications of cancer chemotherapy can be minimized by taking certain precautions, using newer targeted drugs, newer drug delivery systems, techniques and managing them may reduce the burden of anticancer drug's toxicity. Despite lots of progress in drug discovery and development we are still lacking in manufacturing drugs, which selectively kill only cancer cells and cause no harm to other cells, till then improved methods of preventing them will be under continuous search.

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