

Management of Side Effects from Chemotherapy

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Introduction

Chemotherapy is an important modality in cancer treatment. Chemotherapy drugs act by damaging high proliferating cells. By virtue of differences in both biological and proliferation characteristics, chemotherapy causes a greater proportion of cell death among neoplastic as opposed to normal cells. Damage to normal cells result in chemotherapy toxicities and side effects, it can be seen that those actively dividing tissues such bone marrow, hair follicles and gastrointestinal mucosa are most vulnerable.

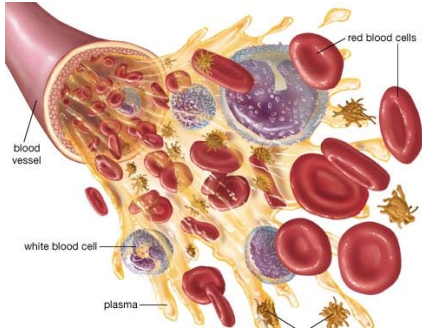
Side effects of chemotherapy range from mild, like non-specific tiredness to life-threatening as in neutropenic fever. They can be classified into haematological, gastrointestinal, dermatological, renal, pulmonary, cardiac, neurological, hepatic and gonadal toxicities. It is important that doctors and nurses are knowledgeable regarding the drugs' adverse effects and expected time of occurrence, and know how to prevent, minimize and manage them. Patients and families education is also important, as many side effects will occur when the patient is at home. In managing side effects, assessment for patient's tolerance to the prior dose and early intervention play a pivotal role in a patient's outcome. To minimize or prevent toxicity, chemotherapy will only be administered if there is adequate baseline blood picture, renal and liver functions, no contraindication with regard to underlying medical conditions, and for certain chemotherapeutic agents, further chemotherapy is discontinued if cumulative doses have reached tolerance levels. In this booklet, medical aspects in prevention and management of chemotherapy side effects will be discussed along with some non-pharmacological measures.



Haematological

White blood cells (specifically neutrophils), red blood cells and platelet are the three main components of bone marrow; they are responsible for protecting the body from infection, transporting oxygen in the circulation and blood clotting mechanism respectively.

Chemotherapy causes bone marrow suppression resulting in neutropenia, anaemia and thrombocytopenia.



Neutropenia

Neutropenia is defined as an absolute neutrophil count (ANC) less than cells/mm^3 . Neutrophil counts usually drop to its lowest level on day 7-14 post-chemotherapy for majority of the chemotherapy regimens, which is commonly referred as nadir. There is an inverse relationship between the degree and duration of neutropenia and risk of infection. Patients with an $\text{ANC} < 100 \text{ cells}/\text{mm}^3$ or those with prolonged neutropenia (> 7 days) are at significantly higher risk for serious infection.

For afebrile neutropenic patients, the goal is to prevent infectious complication or detect infection at the earliest possible stage and promptly intervene. Patient and family education should include:

- Explanation of the function of white blood cells
- Meaning of nadir
- Instructions for temperature taking
- Signs and symptoms of infection (e.g. fever, malaise, those related to specific organs such as cough, urinary frequency with or without dysuria, etc.)
- Hygiene practices emphasizing hand washing
- Identification and assessment of high-risk areas for infection (chest, urinary tract, skin)
- Care of access devices (e.g. Hartman line, urinary catheter)
- Avoidance of exposure to persons with communicable or infectious illnesses, stay away from crowds and animals
- Maintain nutritional status by a balanced diet
- Specific directions for access to healthcare systems (clinic or A&E if emergency)

Febrile neutropenia (FN)

Fever is defined as a single oral temperature of $\geq 38.3^\circ\text{C}$ (101°F) or a temperature of $\geq 38.0^\circ\text{C}$ (100.4°F) for $\geq 1\text{hr}$. The development of fever in a neutropenic patient represents an urgent clinical problem requiring prompt assessment and intervention. More than half of patients will not exhibit any other signs or symptoms of infection. Besides empiric antibiotic therapy, suggested guidelines for care of the hospitalized neutropenic patient include the following:



- Wash hands frequently and thoroughly; this is the single most important measure in preventing infection. Use clean, disposable gloves with each patient
- Place patient in a private room

- Avoid persons with viral or contagious illnesses
- Clean and disinfect equipment before patient contact and after each use

Anaemia

Anaemia presents with symptoms of dyspnoea, dizziness, headache and palpitation. Apart from direct effects of cytotoxic drugs, other factors that contribute to anaemia in a cancer patient include diminished nutritional stores, anaemia of chronic disease, blood loss, cumulative marrow suppression associated with prior treatment, decreased erythropoietin production, etc. A thorough laboratory assessment is recommended to identify the cause of the anaemia. Red blood cell transfusion or human recombinant erythropoietin are the treatment options. Generally, blood transfusion is indicated for an acute need, such as blood loss or symptom severity that warrants prompt intervention. For an average adult, one unit RBC transfusion raises the haemoglobin by 1g/dl. Human recombinant erythropoietin has been shown to decrease the need for transfusion support, and improves quality of life for patients on chemotherapy. Since not all patients will benefit, patients should be monitored and assessed at regular intervals for response and decisions to continue or discontinue.

Thrombocytopenia

Thrombocytopenia (platelet count of less than $100,000/\text{mm}^3$, or $100 \times 10^9/\text{L}$) is a potential or actual dose-limiting side effect for a number of chemotherapy agents. Some cytotoxic agents e.g. carmustine, lomustine, exhibit delayed-onset thrombocytopenia and have a cumulative dose effect. Increased risk of bleeding is the most significant outcome of a reduced platelet count. A moderate risk of bleeding exists when the platelet count falls to less than $50,000 \text{ cells}/\text{mm}^3$, and major risk is associated with platelet counts less than $10,000 \text{ cells}/\text{mm}^3$.



Clinical manifestations include easy bruising, petechiae, purpura, gum bleeding and hypermenorrhoea. To prevent or minimize bleeding in patients with a moderate to severe risk, the following guidelines for practice are recommended:

- Avoid intramuscular injections
- Avoid trauma
- Decrease the patient's level of activity
- Avoid drugs that alter platelet function or clotting (e.g. aspirin and non-steroidal anti-inflammatory drugs and anticoagulants; certain herbs)
- Pressure should be applied for at least five minutes with a pressure bandage for all IV injections, venipunctures, and bone marrow procedures
- Patients should avoid blowing their noses and sneezing. For shaving, an electric razor is recommended

Gastrointestinal

Gastrointestinal side effects include nausea and vomiting, anorexia and taste changes, oral mucositis, diarrhoea and constipation.

Nausea and vomiting



Nausea and vomiting have been ranked the first and second worst side effects of chemotherapy from the patient's point of view. Indeed, some patients fear vomiting so much that they are reluctant to undergo chemotherapy. Therefore, control of emesis must be a priority for all patients undergoing chemotherapy. Female, especially with history of emesis in pregnancy, young age, non-drinker and poor emetic control during prior treatment are risk factors for chemotherapy-induced nausea and vomiting.

There are three patterns of nausea and vomiting associated with chemotherapy: acute, delayed, and anticipatory. Acute nausea and vomiting occurs within the first 24 hours of therapy (usually within 1 to 2 hours) and is generally most severe during the initial 4 to 6 hours. The incidence and severity of nausea and vomiting are related to the emetogenic potential of the drug (Table 1). Knowledge of emetogenic potential of drugs is the basis for choosing the appropriate antiemetics for patients. Delayed emesis has been arbitrarily defined as occurring 24 or more hours after chemotherapy and may last from one to seven days. It is most commonly associated with cisplatin, carboplatin, cyclophosphamide, and doxorubicin. Delayed or residual nausea and vomiting occurs even when antiemetics are effective in preventing acute symptoms within the first 24 hours. Anticipatory emesis is the experiencing of nausea and/or vomiting before receiving another chemotherapy treatment. It is a conditioned or learned response to previous effects from therapy and associated environmental stimuli, in most instances, it was associated with a prior experience when there was inadequate control of emesis. Therefore, patients must be given optimal antiemetic regimen with their initial course of chemotherapy to prevent acute and delayed emesis, and, consequently, anticipatory emesis. Breakthrough emesis refers to nausea or vomiting despite optimal prophylactic pretreatment and/or delayed therapy.

General principles for successful anti-emetic therapy for chemotherapy-induced nausea and vomiting include:

- Aggressive therapy for chemotherapy-naïve patients
- Adequate duration of coverage with antiemetics for the predicted risk period of symptoms
- Appropriate selection of agents and dosing according to the emetic potential of the chemotherapy

Oral mucositis

The onset of oral mucositis or stomatitis typically occurs 5 to 7 days after chemotherapy, and healing occurs 10 to 14 days after cessation of therapy. Indirect effects on the oral mucosa occur 12 to 14 days after chemotherapy, during the granulocyte nadir. Patients may be at risk for local infection. Mucositis causes mild to severe discomfort, affects fluid and nutritional intake, and interferes with speech.

The goal of care for patient at risk or with mucositis is to maintain the integrity of the oral mucosa, prevent secondary infection, provide pain relief and maintain dietary intake. Dietary guidelines for maintain nutritional status for patients with oral mucositis are:

- Avoid foods that are irritating to oral mucosa, especially spiced, acidic, or salted foods
- Use blenderized foods if necessary. Avoid extremely hot or cold foods
- Take extra calories with powdered milk or dietary supplements
- Encourage fluids. Fruit juices may be soothing to oral mucosa and add extra calories



Patients should maintain a high protein diet

Diarrhoea

The GI tract is susceptible to chemotherapy toxicity because of the rapid turnover of the mucosal cells. The agents most commonly associated with diarrhoea are capecitabine, 5-fluorouracil (especially in high dose or in combination with leucovorin or oxaliplatin), irinotecan, methotrexate and topotecan. Irinotecan is specifically associated with early (within 24 hours) and late onset (3 to 11 days post therapy) diarrhoea. Early onset diarrhoea, often preceded by diaphoresis and/or abdominal cramping, can be ameliorated by the administration of atropine.

Anorexia and taste changes

Cytotoxic drug therapy can cause anorexia. Patient may experience metallic taste after drug therapy, a general loss of taste for food. For patients who experience a loss of sense of taste, a variety of simple interventions can be helpful such as sucking on sour candies, using aroma to improve appeal of food, use of plastic utensils if food tastes metallic, and chewing sugar-free gum. Dietitian advice and nutritional support are given to patients with anorexia. The importance of eating despite anorexia should be emphasized, with food intake identified as a component of the treatment plan.

Dermatological

Dermatological toxicity can be local and systemic. Local toxicity occurs in the tissues surrounding the site of drug administration and is described by a variety of venous and cutaneous responses: phlebitis, urticaria, pain, erythema, vein discoloration, and tissue necrosis secondary to extravasation of a drug. Hair loss is the most common systemic manifestation. Other systemic dermatological effects include dermatitis, nail changes, hyperpigmentation, urticaria, photosensitivity reactions, hand-foot syndrome, and radiation-recall reactions.



Alopecia

The actual experience of complete or nearly complete hair loss has often been described by patients as the most devastating side effect of chemotherapy. Hair is an integral part of physical appearance, and its loss may negatively affect self-image, body image, coping skills, and social interactions. The degree of distress may be minimized by adequate preparation for the loss, possible interventions, and ongoing support from healthcare professionals and family members.

Hair loss from chemotherapy is reversible. Many times hair begins to regrow despite continued therapy, and it is not unusual for new hair to reappear two to three months later. Nurses and doctors should make every effort to provide accurate information and support to patients at risk for hair

loss. Patients are shocked when they experience hair loss unexpectedly, and the purchase of a wig or head covering before loss of more than 50% of hair occurs, may decrease the distress. Interventions to help maximize patient adjustment and minimize the distress associated with hair loss include the following:

- Explain to patient the rationale for the occurrence of alopecia, the relative incidence, and the degree of hair loss expected specific to the chemotherapy drug (s) prescribed
- Encourage the patient to express emotions regarding the information provided
- Reiterate the fact that hair regrows and that changes in colour and texture may occur (e.g. curly or gray)
- Discourage the use of dryers, hot rollers, and curling irons, since they may facilitate increased hair loss
- Protect the head from the sun with a hat or sunscreen for complete or nearly complete alopecia
- Maintain scalp cleanliness and conditioning after total alopecia
- Suggest to cut the hair short before chemotherapy, or use of wigs, caps or scarves if wish

Extravasation and its management

Potential local toxic effects from chemotherapeutic drugs range from transient local discomfort during administration to severe tissue necrosis with potential damage to tendons and nerves. Chemotherapeutic drugs have been described as irritant and vesicant. An irritant is a drug that causes local venous response, patient may complain tenderness along the vein and may be accompanied by erythema, which are usually short-lived and subsequent tissue damage is uncommon, and necrosis does not occur.



Gonadal

Chemotherapy causes gonadal dysfunction, resulting in sterilization or decreased fertility. In men, cytotoxic drugs induce reduction in sperm counts during chemotherapy, which can be temporary or prolonged, depending on the nature of the cytotoxic agent and dose. In women, chemotherapy can cause destruction of oocytes, which can lead to ovarian failure and premature menopause. The chance of having early menopause increases as the age increases.

Before initiating chemotherapy, patients should be informed of the potential risk of sterility from the planned cytotoxic therapy and semen cryopreservation is offered to all male patients interested in having children after the completion of cytotoxic therapy.



During treatment, sexual relations between partners may continue, but reliable contraceptive methods should be used. If conception does occur during the course of treatment, the couple should be informed of the risk and evaluate the continuation of pregnancy. It is recommended that patients wait 6 months after the end of therapy before

attempting to conceive. If fertility is preserved, the patients should be informed of the high probability of having healthy children. Although there are theoretical concerns about congenital malformations and genetic disease in offspring, the limited data for humans indicate no measurable excess risk above the background level of 4%, but small (less than twofold) increases could have escaped detection. Any pregnancy after therapy should be monitored (with ultrasound and possibly amniocentesis) because of the potentially increased genetic risk. Women should also be told about the risks of chemotherapy-induced premature menopause. If this does occur, it is important to present a balanced discussion of potential benefits of prompt initiation of hormone replacement (increased bone mineral density and reduced incidence of fracture) as well as risk (cardiovascular disease and breast cancer) so that an individually appropriate decision may be reached. If a woman has an intact uterus, estrogen should be combined with progesterone to prevent endometrial hyperplasia and cancer.