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Chapter 20

# Supportive and Palliative Care in Solid Cancer Patients

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Additional information is available at the end of the chapter

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## 1. Introduction

### 1.1. Cancer background

During this century, cancer has become one of the major problem and diseases which has caused predominant death and it will even surpass heart diseases. Many of the researchers begin to use the term lifetime risk for cancer patients which refer to the time that cancer will progress and developed or the time that the patient will die because of cancer. There are many problems (i.e., side effects) associated with cancer diseases either solid type or hematological type such as nausea, vomiting, diarrhea, constipation, hypercalcemia, pain, lost of appetite, anemia, fatigue, cachexia, leucopenia, neutropenia and thrombocytopenia. However the major problems are nausea and vomiting, neutropenia, anemia, thrombocytopenia and hypercalcemia. Hence due to these reasons cancer is consider as one of the major diseases that will effect on the quality of life for human [1-6].

### 1.2. Chemotherapy background

Chemotherapy was developed and used since the Word War I from the chemical weapon program of the United State of America (USA). Since then chemotherapy has became as one of the most important and significant treatment of cancer. Its main mechanism of action is by destroying the cancer cells which are characterized by their high multiplication and growth speed. However when comparing chemotherapy with other types of treatments, it still remain potentially high risk with many side effects which are difficult to manage. Chemotherapy used required the involvement of various clinical professionals during its various stages of administration and enormous patient health care is needed to overcome its side effects [7-8].

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### 1.3. Chemotherapy side effects

The goal of chemotherapy is to be as effective as possible with tolerable side effects, since the dose of chemotherapy will be toxic to the cancer cells as well as to the normal cells. A proportion of the cancer patients suffer from only mild side effects whereas others may suffer from serious side effects. These side effects are classified as:

1. Acute, which develop within 24 hours after chemotherapy administration.
2. Delayed, which developed after 24 hours and up to 6 to 8 weeks after chemotherapy treatments.
3. Short term, combination of both acute and delayed effect.
4. Late/ long term, which developed after months or years of chemotherapy treatment.
5. Expected, which developed among 75% of the patients.
6. Common, occurred in 25%-75% of the patients.
7. Uncommon, happened is less than 15% of the patients.
8. Rare, occur in only 5% of the patients.
9. Very rare, occur with less than 1% of the patients.

Occurrence of specific side effects will vary according to the chemotherapy or medications used. The most common side effects experienced are nausea and vomiting, anemia, hair lost, bleeding (thrombocytopenia), hyperuricemia, neurotoxicity, cardiotoxicity, bone marrow depression, alopecia, nephrotoxicity, pulmonary toxicity, dehydration, cystitis and mucositis. So different parameters must be taken into consideration to prevent, reduce and overcome these side effects [8-10]. This chapter will focus on the main side effects caused by cancer disease and/ or chemotherapy.

## 2. Main problems caused by cancer disease itself and/ or chemotherapy treatment

### 2.1. Nausea and vomiting

Both nausea and vomiting are recognized as two separate and distinct conditions. Nausea is an unpleasant sensation of being vomit or urge to vomit which may or may not result in vomiting. While, vomiting or emesis is the process of expelling of undigested food through the mouth. Nausea and vomiting can arises from different or wide spectrum of etiologies which are either directly associated to cancer disease itself or to its treatment. According to the new ranking of chemotherapy side effects, nausea is the number one or the most disturbing side effect while vomiting is the third and sometimes the fifth disturbing chemotherapy side effects. Even so, not all cancer patients suffer from nausea and/ or vomiting because not all of them were treated with emetogenic chemotherapy [11-17].

*2.1.1. Nausea and vomiting in solid cancer patients*

Nausea and vomiting are two of the major problems that are associated with cancer patients and 50%-55% of cancer patients suffer from both nausea and vomiting even with the use of antiemetic drugs. The main causes for this are either due to the chemotherapy or because of the cancer progression. Some of the cancer patients who were treated with chemotherapy did not suffer from nausea or vomiting because the chemotherapy used were not significantly emetogenic. Nausea and vomiting still remain the major side effects that occur and are associated with chemotherapy and cancer diseases [11, 18-20].

*2.1.2. Understanding nausea and vomiting in advanced solid cancer*

Both nausea and vomiting are very common problems especially with advanced stages of solid cancer diseases like breast cancer and stomach cancer where 50 to 60% of the patients are mainly female under 65 years of age [21]. In this situation, nausea and vomiting occur because of the advanced stages of solid cancer diseases characterized by more severe complications than that caused by chemoradiotherapy or other treatments. The main causes for those problems are gastric stasis, obstruction of the intestine, opioid use, constipation caused by morphine uses, hypercalcemia, brain metastasis, renal failure, hyponatremia, increases in the intracranial pressure and tumor burden [21].

*2.1.3. Pathophysiology of chemotherapy-induced nausea and vomiting*

Chemotherapy cause nausea by stimulating the autonomic nervous system (ANS), while vomiting is triggered when afferent impulses from chemoreceptor trigger zone (CTZ), pharynx, cerebral cortex and vagal afferent fiber stimulate the vomiting center (VC) located in the medulla. The stimulation of the VC leads to contraction of muscles of abdomen, chest wall and diaphragm, so this will lead to an expulsion of stomach and intestine contents [11-20]. The main mechanism of chemotherapy induced vomiting is the stimulation of the entrochromaffin cells lining the wall of the gastrointestinal tract (GIT) hence causes the release of the serotonin. The serotonin will then bind to the vagal afferent 5-$HT_3$ receptors in the GIT which will send impulses to the CTZ and VC. Vomiting will be triggered when afferent impulses from CTZ, pharynx, cerebral cortex and vagal afferent fiber transfer impulses to the VC [22].

*2.1.4. Major patients risk factors related with nausea and vomiting*

1- Gender, 2-Age, 3- History of motion sickness and history of vomiting during pregnancy, 4-History of drinking alcohol, 5-Patient anxiety [11, 16, 18, 23-25]

*2.1.5. Major chemotherapy factors responsible for incidence of nausea and vomiting*

There are several chemotherapeutics factors that play a major role in the incidence and severity of both nausea and vomiting which are:

1- Emetogenic potential of the drug, 2- Dosage level, 3- Schedule of administration, 4- Route of administration, 5- History of previous chemotherapy, 6- Rate of I.V infusion [11, 16, 18, 23, 26].

*2.1.6. Classification of chemotherapy induced nausea and vomiting*

This classification is based on the emetogenic potential of the chemotherapeutic drug.

1. Severe (90% of the patients will experience nausea and vomiting) Example: Carmustine I.V ≥ 250 mg/ $m^2$, Cisplatin I.V ≥ 50 mg/ $m^2$, Cyclophosphamide I.V > 1500 mg/ $m^2$, Dacarbazine, Mechlorethamine, Nitrogen mustard and Streptozocin.
2. High (60%-90%) Example: Carboplatin, Carmustine I.V ≤ 250 mg/ $m^2$, Cisplatin I.V < 50 mg/ $m^2$, Cyclophosphamide I.V 750 mg/ $m^2$ to 1500 mg/ $m^2$, Cytarabine I.V > 1gm/ $m^2$, Dactinomycin, Daunorubicin, Doxorubicin I.V > 60 mg/ $m^2$, Irinotecan, Methotrexate I.V > 1 gm/ $m^2$ and Procarbazine PO dose.
3. Moderate (30%-60%) Example: Altretamine I.V PO dose, Asparginase, Cyclophosphamide (I.V) ≤ 750 mg/ $m^2$, Cyclophosphamide PO dose, Doxorubicin (I.V) 20 to 60 mg/ $m^2$, Epirubicin I.V, Idarubicin, Ifosfamide, Lomustine PO dose, Methotrexate (I.V) 250-1000 mg/ $m^2$, Mitoxantrone (I.V) < 15 mg/ $m^2$, Pemetrexed, Raltitrexed, Temozalamide and Topotecan.
4. Low (10%-30%) Example: Aldesleukin, Amsacrine, Bortezomib, Capecitabine, PO dose, Docetaxel, Doxorubicin liposomal, Etoposide all dose I.V or PO, Erlotrinib PO dose, Fluorouracil, Gefitinib PO dose, Gemcitabine, Methotrexate (I.V) 50-250 mg/ $m^2$, Mitomycin, Paclitaxel, Porfimer, Teniposide and Trastuzumab.
5. Very low (less than 10%) Example: Bleomycin, Busulfan PO dose, Chlorambucil PO dose, Cladribine, Fludaradine, Hydroxyurea PO dose, Interferon, Levamisole, Melphalan PO dose, Methotrexate < 50mg/ $m^2$, Rituximab, Thalidomide, Thioguanine, Thiotepa, Vinblastine, Vincristine, Vinorelbine and Vindesine [25, 27].

*2.1.7. Classification and incidence of chemotherapy induced nausea and vomiting*

CINV are clinically classified as:

1- Acute chemotherapy related nausea and vomiting, 2- Delayed emesis, 3- Anticipatory emesis [11, 16, 18, 28].

*2.1.8. Nausea and vomiting treatment options*

The main goal of the antiemetic treatment is to abolish nausea and vomiting which in the last twenty years consider as an inevitable chemotherapy side effect. This prevention is focused on the entire period of emetic risk which is 4 days for patients who received highly or moderately emetogenic chemotherapy [22, 29]. This could be perfectly achieved by understanding the mechanisms of these antiemetic drugs either alone or in combination so as to get their maximum benefit [30]. Modern antiemetic treatments help in prevent-

ing 70%-80% of nausea and vomiting problems. Combination antiemetic treatment becomes the standard regimen used for the control of nausea and vomiting caused by chemotherapy [30]. The different types of treatments are as follows: Serotonin-receptor antagonists (*5-$HT_3$*), Dopamine-2-receptor antagonists, Corticosteroids, Neurokinin-1-recptor antagonists, Cannabinoids & Benzodiazepines [29].

*2.1.9. Genetic polymorphism and incidence of nausea and vomiting*

Interindividual diversity in drug metabolism is caused by many factors including environmental factors, cultural factors related with type of diet, concomitant drug therapy as well as genetic factors i.e., ethnic variation. All of these variations play an important role in changing pharmacokinetic and pharmacodynamic properties, volume of distribution, elimination, disposition and clinical effect for many drugs [31, 32]. Much of this distinction has shown to be caused by genetic polymorphisms of the human cytochrome P450 enzymes (CYP) [32]. CYP is the most vital enzymatic system concerned with drug metabolism. Approximately 65% of common drugs used are metabolized by cytochrome P450 enzymes and half of them are mediated by the CYP3A subfamily [32].

**2.2. Anemia**

This is a condition characterized by lack of blood or in other word a reduction of total quantity of erythrocyte (red blood cells, RBC) or hemoglobin in the circulation which are necessary for normal function. This is caused by the inability of the bone marrow to replace the erythrocyte lost. The normal level of RBC for the male is $5.4\times10^6$ cell/ μl and for female is $4.8\times10^6$ cell/ μl [11, 33-35]. It is considered as one of the most frequent hematological demonstration of malignant diseases, which will lead to momentous impairment in every tissues and organs of cancer patients and put them under serious stress. This major problem may arise because of the underlining diseases (i.e., cancer diseases) or radiotherapy or chemotherapy treatment received [36, 37].

*2.2.1. Red blood cell (RBC) and iron*

The large proportion of body iron (20 mg per day) is used in the synthesis of erythrocyte cells. The body absorbed about 1 mg of iron per day from the gut to compensate the amount of daily iron lost. After the transition from erythroblast to reticulocyte, it will then remain for 3 to 4 days in the bone marrow after which being released into the blood circulation and circulate for about 100-120 days. Red blood cell (RBC) has no mitochondria so are totally dependent on ATP generated during glycolysis process. In the circulation RBC loss about 20% of its hemoglobin and shows physiological steps of aging. They will be phagocytes by the macrophage leading to destruction of the erythrocyte and the removal of the iron from the hemoglobin (Hb) which will be released into the plasma and redistributed again [38].

*2.2.2. Types of anemia*

There are different types of anemia as follows:

1- Iron deficiency anemia, 2- Folic acid deficiency anemia, 3- Vitamin (Vit) $B_{12}$ deficiency anemia, 4- Vit C deficiency anemia, 5- Hemolytic anemia. It is an acquired type of anemia, 6- Thalassemias, 7- Sickle cell anemia, 8- Anemia of chronic diseases (ACD) [36, 37].

*2.2.3. Erythropoietin (EPO) description and action*

EPO is a glycoprotein hormone consists of 165 amino acid with a peptide mass of 18.2 kDa. It is mainly produce by the liver during fetal stage but after birth the kidneys become the primary production sites. It has been realized that most of EPO in the circulation comes and produce from the cortex of the kidney [39]. EPO production is mainly controlled by the feedback system between kidney and bone marrow. The kidneys mainly depend on the renal oxygen sensor for EPO production. Kidney cells response greatly towards hypoxia by increasing the EPO production. Serum level of EPO ranges between 10 to 20 mU/ mL and for normal situation the observed EPO concentration/ predictive EPO concentration (O/P) ratio must range between 0.8-1.2 [41]. EPO maintain erythropoiesis is by preventing the colony forming unit-erythroid (CFU-E) from death by apoptosis process. By this way these progenitor cells will keep proliferating and differentiating to produce erythrocyte [39].

*2.2.4. Causes of anemia of chronic diseases (ACD)*

Anemia remain as one of the serious and frequent problem of cancer mainly cancer of the gastrointestinal, liver, head and neck, ovarian and cervix. This is mainly caused by cytokines including interlukine-1, interlukine-6, interferon-$\gamma$ and tumor necrosis factor-$\alpha$ produced by these cancer diseases. These cytokines caused impairment of erythropoietin (EPO) synthesis, reduce erythrocytes life span and prevent normal iron utilization. Other direct effect of tumor that cause anemia is bone marrow replacement which is associated with inhibition of the body ability for the production of RBC. This condition of bone marrow suppression is associated with specific types of cancers like breast, prostate, myeloma, lymphoma and acute leukemia. Also bone marrow suppression is mainly caused by chemotherapy and radiotherapy which are the main treatment for cancer. Mainly in cancer patients the major risk factors responsible for incidence and severity of anemia are the form of cancer as well as type and dose of chemotherapy administered to the cancer patients. [11, 33-36, 40, 41].

*2.2.5. Diagnosis of anemia*

Several parameters need to be checked for anemia diagnosis since each one is considered important and they are as follow: Family history, laboratory tests, X-ray, biopsy and bone examination [33, 35, 42].

*2.2.6. Grades of anemia (levels)*

The grades or severity of anemia will depend on several factors like hemoglobin level, velocity of onset of anemia, age, co-morbidities, extent of the underlining malignancy, intensity of treatment and the biological function of the patients organ. Anemia grades as follows:

Normal level (women Hb= 12.0 g/ dL-16.0 g/ dL, men Hb= 14.0 g/ dL- 18.0 g/ dL)

Mild Anemia Hb= 10g/ dL

Moderate Anemia Hb= 8.0 g/ dL- 10.0 g/ dL

Severe Anemia Hb= 6.5 g/ dL- 7.9 g/ dL

Life Threatening Anemia Hb= < 6.5 g/ dL [33, 36, 43].

*2.2.7. Clinical signs and symptoms of anemia in cancer patients*

The severity of signs and symptoms of anemia depend on several factors like Hb level, age, extent of the underlining malignant, comorbidity, rate of anemia onset, biological activity of patients vital organs and intensity of treatment used for anemia. Generally in elderly patients the clinical signs and symptoms appear with Hb level higher than that in younger patients. These symptoms usually appear gradually, starting with fatigue which is considered as one of the major signs happing in 60% to more than 90% of the anemic patients. Lethargy and lost of concentration will also take place as the Hb becomes lower than 12 g/ dL. When anemia becomes severe and chronic this will lead to decompensation of cadiorespiratory and impairment of several body organs and activities [36, 46].

*2.2.8. Role of cancer patients ages*

It has been found that the incidence of anemia and cancer increases as the age of the patient increases too. Anemia is much more related and significantly present as the age became higher than 60 years old and with steeper increases after age 80 years. Many studies showed that the hemoglobin levels remain stable between age 60 to 98 years old but there are several causes for the high incidence of anemia in the old age since there were high comorbidity, hematopoietic stress and reduce in function of many vital organs. For this reason there will be great association and increases in occurrence of anemia in elderly patients [44].

*2.2.9. Cancer patients gender and anemia*

As mention above anemia highly occur in patients older than 60 years old, but it has been found that among women, anemia happen at a younger age. The main difference between men and women are the presence of menstrual cycle i.e., blood loss and childbearing iron loss which make incidence and association of anemia higher in younger women as compared to men [44]. Besides that men and women who do not have menstruation, the amount of iron lost in one day is 1 mg. While, in women still with menstrual, the loss is about 0.6 to 2.5 times more than previous mentioned amount. The amount of iron lost during each menstruation cycle depends on the severity of bleeding. The standard iron lost per menstrual cycle for woman weighting about 60 kg is about 10 mg. So all of these evidences showed that anemia is associated with female as a gender more than male [45].

*2.2.10. Cancer patients race*

Race also play an important role in incidence of anemia since it is consider as one of the risk factor which play role in its occurrence. The prevalence of anemia in USA among white women

is 7.1% and 25.1% among black women even after adjustment of iron level. Besides that black women are characterized by lower mean hemoglobin level compared to white women. Also black woman has a wide standard deviation in mean of hemoglobin than the white one has [45].

*2.2.11. Mechanisms of anemia in cancer patients*

*2.2.11.1. Role of cancer disease*

Occurrence and association of anemia with cancer depends on several factors including patients age, stage of cancer, presence or absence of infection and other comorbidities. Anemia prevalence is highly associated especially with lymphomas, genitourinary tumor, lung and multiply myeloma. The incidence of mild to moderate anemia with solid tumor is higher than incidence of severe anemia which occurs highly with hematological cancers than solid one [36, 46, 47]. The main mechanism whereby cancer causes anemia is by producing cytokines which are mainly tumor necrosis factor (TNF-$\alpha$) and interleukin-1 and they have the ability to hamper EPO production and action, reduce the life span of RBC and preclude ordinary utilization of iron. Other mechanisms which will cause association of anemia with cancer will be separated from the cancer itself like Vit $B_{12}$, folic acid and iron deficiency. Renal, endocrinal disorders splenomegaly, clonogenic and cachexia occurrence with cancer also play a major role in occurrence of anemia [36].

*2.2.11.2. Role of chemotherapy*

Anemia is one of the common side effect of chemotherapy especially with the myelosuppressive type. Incidence and severity of anemia depend on several different factors which are the chemotherapy type, schedule and intensity as well as type of cancer. Chemotherapy cycles also play an important role in increasing the severity of anemia since multiply cycles will cumulatively inhibit or reduce erythropoiesis. It has been found by the European Cancer Anaemia Survey (ECAS) that the incidence of anemia after the first cycle is 19.5% and after second cycle is 34.3% while after the third the incidence was more than 40%. Also single or combination chemotherapy play a serious and major role in anemia incidence and severity since the use of combination chemotherapy regimen will leads to severe anemia more than the use of single chemotherapy drug [48-50]. Besides chemotherapy myelosuppression, anemia can take place as a result of direct destruction of the RBC (i.e., direct effect on the erythropoiesis in the bone marrow) or reduced erythropoietin production (i.e., impact on EPO production). When this chemotherapy drug or other drugs used repetitively this may lead to prolong production of anemia. Also the results that obtained from clinical trials showed that the probability of mild anemia incidence after the use of chemotherapy is 100%, while the probability of severe anemia incidence after chemotherapy is 80%. From these results and data it has been proven that chemotherapy is the major impact factor for anemia onset and severity in cancer patients [41, 48, 51-53].

*2.2.12. Indications and options for anemia treatments*

Anemia and its related symptoms have serious negative effects on patients quality of life (QOL) and anticancer treatment since it will leads to treatment delay. These effects may be tolerated in young patients even with very low hemoglobin levels. While in patients with multimorbidity would not be able to tolerate this and as a result of that many severe clinical signs and symptoms will developed even with minor reduction in the Hb levels [36, 54, 55]. The treatment strategies of anemia mainly based on the clinical situation, clinical signs and symptoms and on the underlining cause of anemia. These treatments will include red blood cell transfusion, corticosteroids, VitB12 and Epoetin alfa (recombinant human erythropoietin, rHuEPO). All these treatments were used to overcome anemia related signs, symptoms and to improve the anemic patients (QOL) [36].

**2.3. Thrombocytopenia**

Thrombocytopenia is a term used to denote abnormal decrease or drop in platelets numbers. The main function of these platelets is clot formation during bleeding in order to prevent blood lost. Thus a decrease in platelet number will leads to bleeding condition which ranges from mild bleeding from small blood vessels to severe bleeding from large blood vessels. Severe bleeding in the presence of severe thrombocytopenia or when is coupled with other clotting disorders can leads to serious morbidity or death. Thrombocytopenia is a common problem experience by cancer patients, which usually resulted from the use of conventional chemotherapy and at times is a dose limiting factor for chemotherapy administration. The incidence of thrombocytopenia among solid cancer patients is rather low i.e., ranging between 10%-25% among breast cancer, ovarian and germ cell cancer patients who were treated with intensive chemotherapy. However thrombocytopenia incidence is high among acute leukemia patients [56-63].

*2.3.1. Platelets morphology and structure*

Platelets or thrombocytes are irregular, disc shaped cells which are considered as the smallest cells in the blood (0.5 to 3.0 μm diameter). They are usually produce from the megakaryocytes which are large cells (80 to 150 μm diameter) found specifically in the spongy center of long bones by the stimulation of thrombopoietin (TPO) by process called endomitosis whereby each megakaryocyte cell produce about 2000 platelets. These platelets shared a characteristic of having a very short life span (five to nine days only) so the bone marrow of healthy individual continuously keep producing new platelets cells to replace the old dead ones. The thrombopoietin hormone is mainly synthesis and produce by the liver and plays a major role in stimulation of proliferation and maturation of platelets. The circulating platelets have no nucleus but they have alpha granules and dense granules [57, 64, 65]. Physiologically the platelets are removed from the blood circulation by two mechanisms. The first is being used at common sites of vascular injury like in the microcirculation, secondly to be phagocyte by macrophages cells predominantly in the spleen and liver [66].

*2.3.2. Platelets function*

Platelets have vital functions in immunity, wound repair and homeostasis. These functions mainly depend on platelets concentration in blood circulation. Platelets prevent bleeding by either sealing the hole in the blood vessel wall or by forming haemostatic plug or by liberating several chemicals that will activate more clotting formation by breaking down more of the platelets. The main steps for platelets action to form clot are the following:

1. Adhesion (Step 1): This reaction is mediated by release of granules and characterized by shape change of the platelets from disc shape to spiny spheres after their adhesion to collagen. The aggregation of the platelets in this face is reversible.
2. Aggregation (Step 2): In this step more of platelets adhere to each other and there will be an obvious shape change of these platelets. The main factors that stimulate this step are the chemical changes.
3. Release (Step 3): Here the aggregation caused by the dense granules released by the platelets themselves is irreversible. In addition vasoconstriction will take place as a result of thromboxane $A_2$ released by the platelets.
4. Stabilization of the clot (Step 4): This is the main reaction which is responsible for the thrombus formation, whereby the aggregate platelets will release factor V that will accelerate the aggregation of other platelets and this will lead to stabilized clot formation [64, 67].

From this it is clear that thrombocytopenia which is associated with decrease in platelets count in the blood of cancer patients such as leukemic patients is considered as a very serious problem. Thrombocytopenia prevalence in hematological patients is very high. While in case of solid tumor, thrombocytopenia happens because of chemotherapy uses and thus the incidence is rather low. However in some subgroups the incidence is higher than 20% and it still remain as a serious and dangerous problem [62].

*2.3.3. Thrombopoietin hormone (TPO)*

It is a single 353- amino acid protein, synthesized primarily in the liver. Its level will increase during thrombocytopenia and keep increasing in response to the decline in platelet mass. For this reason most of the studies found that when platelets is transfused to the thrombocytopenic patients the TPO level will decreased. TPO mainly act by increasing the numbers of megakaryocyte colony forming cells (Meg-CFC), increases their ploidy, size and growth to produce more of the platelets. Moreover, it will stimulate the hematopoietic stem cell of the bone marrow and it has been found that high doses of TPO will lead to reactivation of the mature platelets to some aggregation stimuli [61].

*2.3.4. Main causes of thrombocytopenia*

The main causes leading to occurrence of thrombocytopenia are:

1. Chemotherapy drugs.

2. Solid cancer.
3. Blood cancer (Leukemia).
4. Spleen cancer.
5. Anemia.
6. Hemorrhage which will lead to increases loss of platelets.
7. When the rate of platelets destruction is higher than the rate of bone marrow platelets production [57, 59, 65].

*2.3.5. Role of age and gender*

Repetto (2003) mentioned that anemia is highly prevalent and happened in the elderly cancer patients who receive chemotherapy. This is specifically because their senescent cells have low ability to repair DNA and their low mass of the hematopoietic stem cell causing slowing of their recovery ability. Repetto also mentioned in his study that the occurrence of grade 3 thrombocytopenia is highly associated with older female suffering from breast cancer and found that there is an association between age and gender with thrombocytopenia. While others retrospective studies of solid tumor patients found that there is no association between age and myelosuppression i.e., neutropenia, anemia and thrombocytopenia occurrence [68].

*2.3.6. Chemotherapy and thrombocytopenia*

Thrombocytopenia is a detrimental side effect of chemotherapy since it will lead to hemorrhage from vital organ particularly the brain specifically within solid cancer patients who were treated with chemotherapy. These chemotherapies caused thrombocytopenia by different mechanisms either by suppressing megakaryopoiesis leading to prevention of platelets production or by direct damaging of the platelets. Chemotherapies like antimetabolites and alkylating agents induced severe thrombocytopenia due to their ability in causing bone marrow suppression and specifically after the first cycle of chemotherapy [62, 69, 70, 71].

*2.3.7. Mechanism of thrombocytopenia in solid cancer*

The association between bleeding and thrombocytopenia in patient suffering from leukemia was first described in 1962. Later in 1878 and 1984 this was reported happening among patient suffering from solid cancer [72]. Thrombocytopenia as a serious side effect is usually associated with solid cancer as a result of its metastasis to bone marrow. Theoretically most of solid tumors can metastasis to bone marrow but the most frequent are breast, lung and prostate cancers. These cancers when metastasized to bone marrow will lead to bone marrow suppression resulting in neutropenia and thrombocytopenia with serious morbidity and mortality (Kilickap *et al*., 2007). Besides that Elting and his colleagues mentioned that solid cancer patients are characterized by several things which are poor performance status, low baseline for platelets count and bone marrow metastasis. Despite that the bleeding situation among solid cancer patients remain poor compare with hematological malignant unless all the above characteristic are all present [62].

*2.3.8. Diagnosis of thrombocytopenia*

Different parameters are taken into consideration in order to diagnose thrombocytopenia such as medical history and laboratory test. Platelets count which is considered as part of the complete blood count (CBC) is the main key for the diagnosis of thrombocytopenia. It measures the exact numbers of platelets in a measured volume of blood. If the test shows low number of platelets then a careful examination for spleen and bone marrow biopsy must be done since both have a direct association with thrombocytopenia occurrence. Usually in adults when the platelets count is less than 100,000 cell/ microliter it is considered low but sometimes this happen without any symptoms. Other important tests which are used to diagnose thrombocytopenia are the prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT). The results of these tests play a critical role in the diagnosis and certification of the presence of thrombocytopenia. In addition to liver enzymes test, renal function test, erythrocyte sedimentation rate (ESR), Vit $B_{12}$ and folic acid levels are also carried out [57, 59, 64, 65, 73, 74].

*2.3.9. Grades of thrombocytopenia*

The normal range of the platelets is between 150,000 and 450,000 cells per microliter of blood (i.e., 150-450×$10^9$/ L) while thrombocytopenia could be classified into three levels as follows:

**1.** Mild thrombocytopenia if platelets count < 150 and ≥ 100 × $10^9$/ L.

**2.** Moderate thrombocytopenia if platelets count < 100 and ≥ 50 × $10^9$/ L.

**3.** Severe thrombocytopenia if platelets count < 20 × $10^9$/ L [75, 76].

*2.3.10. Clinical signs and symptoms of thrombocytopenia*

There are several signs and symptoms which occasionally happen with thrombocytopenia. These are bloody stool, dizziness, headache, hemorrhage, oral bleeding, nose bleeding, vaginal bleeding, black stool and petechiae (reddish purple spots in the skin) [57, 58, 74].

*2.3.11. Options for thrombocytopenia treatments*

There are different options for thrombocytopenia treatment but the selection will mainly depends on the etiology and severity of thrombocytopenia. Sometimes with asymptomatic thrombocytopenia treatment is not required like that in children with viral infection. But if thrombocytopenia incidence is because of spleen enlargement then splenectomy will be beneficial and effective in increasing the platelets counts. While for thrombotic thrombocytopenic purpura (TTP) treatment is needed since it can leads to renal failure. In case of idiopathic thrombocytopenic purpura (ITP) the treatment depends on severity of the case and the platelets counts. In the case of heparin induce thrombocytopenia and thrombosis (HITT) the treatment is by stopping heparin administration. If the cause of thrombocytopenia is due to patient's immune system causing destruction to the platelets then the use of corticosteroids is very effective so as to suppress immune response. While if the cause is due to chemotherapy then the decision to either continue the treatment with low chemotherapy doses or use of

alternative drugs or use of platelets growth factors (i.e., thrombopoietic growth factor) (Oprelvekin, Neumega®) should be made. Recombinant human interleukin-11 (rhIL-11) will stimulate megakaryocyte maturation and proliferation and maintain platelets production. It has been proven by the Food and Drug Administration (FDA) that rhIL-11 is very effective in reducing and preventing of severe thrombocytopenia as well as it will decrease the need for platelet transfusions especially after myelosuppressive chemotherapy which could be continue with the same doses. In the case of severe thrombocytopenia (i.e., platelet level ≤ 20,000/ μL) which is due to intensive chemotherapeutics drugs treatment of hematological and solid cancer patients, in this case platelet transfusion is needed. At this point, patient will suffer from severe bleeding and the laboratory tests signify that platelets transfusion is very important and a required treatment. Platelets transfusion is one of the most important treatments for acute and severe thrombocytopenia, but there are some limitations to its use which are: the availability of the blood products since it must be freshly taken and used within 5 days, cost, refractoriness, transfusion reaction and diseases transmission [57-59, 63, 76, 77].

#### *2.3.12. Thrombocytopenia and neutropenia*

Acute thrombocytopenia has been described in patients given Hematopoietic Growth Factors. The main factor which play role in this incidence is neutropenia treatments which are either GM-CSF and/ or G-CSF. This rapid incidence for thrombocytopenia in association with these treatments is mainly because these treatments sometimes target the platelets or caused their destruction. But the main mechanism which is responsible for the incidence of neutropenia with thrombocytopenia together has not been defined yet [78].

### 2.4. Hypercalcemia

Hypercalcemia is a life threatening situation in which serum calcium level is elevated greater than 10.5 mg/ dl, while albumin concentration is lower than 4 g/ dl. It is a serious problem that occurs in about 10%-20% of all cancer patients especially lung, breast, head and neck cancer patients. While, in hematological cancer hypercalcemia also takes place specifically in the advanced phases of both myeloma and lymphoma. Besides that a very important point is that hypercalcemia is mainly caused by cancer without any effect or role from anticancer treatments. So many references consider hypercalcemia as a very serious and dangerous complication that caused a significant morbidity and mortality frequently in breast cancer patients. It can occur in patients with and without bone metastasis and the main cause of hypercalcemia is the pathological bone resorption. Bone resorption is caused by the secretion of cytokine like parathyroid hormone-related protein (PTHrP) leading to activation and differentiation of osteoclast cell. In normal condition normal breast cells also secreted PTHrP during lactation so as to stimulate bone resorption and skeletal calcium release which will be used in milk synthesis. In this situation hypercalcemia is asymptomatic since the elevation of calcium level is mild, but when serum calcium elevation became very high it will leads to significant morbidity and mortality. Hypercalcemia is highly associated with breast cancer more than other types of cancers [78-83].

*2.4.1. Calcium homeostasis*

Calcium in human body has multiply functions, it is one of the major components and mineral of the body skeleton and its concentration is maintained by influx and efflux to the extracellular fluid from kidney, bone and gut. This vital process is regulated by two hormones which are parathyroid hormone (PTH) and 1, 25 dihydroxyvitamin D. Serum calcium consist of calcium bounded to albumin 37%, bounded with globulin (10%), biologically active calcium (47%) i.e., ionized form and calcium complex with anion (10%) (like: phosphate, citrate, bicarbonate). The ionized serum calcium is the only form metabolically active and is regulated by homeostatic mechanisms [87, 90, 98]. Calcium also has other important role in regulation of the cellular metabolism function, since it is a co-factor for many of body enzymes reactions. Also, calcium is needed for cell adhesion, cell death, an important component of cellular electrical current and has a very important function in muscular contraction process [84, 85].

*2.4.2. Kidney role in calcium homeostasis*

Kidney plays a very important role in regulation of calcium concentration in the extracellular fluid and its capacity to clear the calcium is about 600 mg per day (15 mmol/ day). In adult approximately 98% of calcium is resorbed by kidney. This process of calcium absorption is mainly controlled by PTH and 65% of total reabsorbed calcium happens at the proximal tubules, 20-25% in the ascending loop of Henle, while only 10% in the distal convoluted tubules [86].

*2.4.3. Gut role in calcium homeostasis*

The daily amount of calcium absorbed ranges between 150-200 mg/ day and this is send to the extracellular fluid. This process of absorption is mainly regulated by 1, 25 dihydroxyvitamin D hormone and calcium concentration in the blood circulation. Besides that the amounts of calcium absorbed from the daily diet is affected by the amount of calcium in the diet and presence of other dietary components which may serve to increase (lactose, fatty acid) or decreases (oxalate, phosphate and phytate) calcium absorption. The absorption of calcium from the daily diet varies even in healthy adult from 20% to 70%. The main parts responsible for absorption are the ileum (65%) and jejunum (17%). This is because these parts are the longest parts and hence the longest time calcium will be absorbed [87].

*2.4.4. Bone role in calcium homeostasis*

Bone consider as the main storehouse of calcium which store 99% of the body calcium. The role of bone in calcium homeostasis is important in normal conditions since the process of bone formation is tightly coupled with processes of bone resorption i.e., the velocity of calcium influx and efflux between the extracellular fluid and bone. The extracellular calcium concentration will be disturbed when the rates of bone resorption increase more than the rate of bone formation. This is seen in cases of advanced cancer diseases which caused activation of the osteoclast cell of the bone marrow leading to increase in bone marrow destruction and increase in calcium efflux. This mainly happy when the cancer disease metastasis to bone marrow and

is usually consider as a catastrophic situation. Metastasis to bone marrow happens in 30% of breast cancer patients and causing disturbances in the plasma calcium concentration. Thus it is clear that bone play a critical role in the maintenance of serum calcium level [86, 88].

*2.4.5. Main hormones responsible for calcium control*

The extra cellular calcium concentration is maintained in a narrow range of 8.5-10.2 mg/ dL (2.1-2.55 mmol/ L) by two main hormones which are:

**1.** Parathyroid hormone (PTH)

**2.** 1,25-dihydroxy-vitamin D [1,25 $(OH)_2$ D]

Both act on the three main organs which are kidney, gut and skeleton but PTH is more important since it regulate calcium level from minute to minute (i.e., very rapid effect), PTH it is consists of 84 amino acid single chain polypeptides and is mainly secreted by the chief cells of the four parathyroid glands besides the thyroid gland in the neck. PTH secretion is regulated by the serum calcium level of the extracellular fluid. When calcium concentration increases, the PTH secretion will be suppressed and when the calcium concentration decreases, PTH secretion increases. PTH mainly regulates the calcium transportation between extracellular fluids and kidney, bone and gut. PTH has a direct effect on bone and plays a critical role in increasing the rate of bone formation and turnover. Its effect on bone came from its stimulation and activation for the osteoclast cells which will lead to increase in bone turnover and it also increases the rate for bone formation. This effect has been found to be dependent on the presence of other hormones like 1, 25-dihydroxyvitamin D. PTH effect on kidney will leads to an increase in distal tubules reabsorption of calcium. Here its effect is enhanced by 1, 25-dihydroxyvitamin D, but it has no direct effect on the gut [78, 85, 88]. 1, 25 dihydroxy-vitamin D is the major biological active metabolite of vitamin D. This steroid-like metabolite is derived either from skin during its exposure to ultraviolet light (i.e., sun light) or from plant ergosterol after its ingestion in the gut. It increases the absorption of calcium and phosphorus from the gut by active transport as well as it increases the bone resorption. 1, 25 dihydroxy-vitamin D is characterized by its slower action than PTH but it is more effective than PTH in long term control of the serum calcium level [83, 86, 89]. Besides these two hormones, calcitonin which is 32 amino acid peptide also is involved in calcium content. It is synthesis and secreted by parafollicular cells of the thyroid gland. Its main action is by inhibition of the osteoclast cell from resorption of the bone by causing their dissolution to mononuclear cells [85].

*2.4.6. Causes of hypercalcemia*

The main causes of hypercalcemia during solid or hematological malignancy are as follows:

**1.** The direct effect of cancer diseases on the bone by causing bone destruction such as with breast cancer, lung cancer, multiply myeloma and leukemia. Hypercalcemia occurs in about 10%-20% of all cancer patients during specific stages of their malignant diseases. Lung and breast cancers are highly associated with hypercalcemia incidence beside head

and neck cancer. While myeloma and lymphoma are the most common hematological types of cancers associated with hypercalcemia.

2. Some cancers diseases lead to production of parathyroid hormone-related protein (PTHrP) which is mainly associated with solid cancer but not with malignant cancer.
3. Some cancer diseases decrease the ability of the kidneys to remove excess calcium also leading to decreases in the urination.
4. Dehydration due to nausea and vomiting which will lead to difficulties of the kidneys to remove excess calcium from the blood.
5. Decreases in the movement and activity of cancer patients which will lead to breakdown of the bone and hence increase in the release of the calcium into the blood [90-94].

*2.4.7. Hypercalcemia diagnosis*

Diagnosis of hypercalcemia is made based on serum calcium level and also on levels of phosphate, chloride, PTH and alkaline phosphates. Other tests for kidney function especially urea level, creatinine level and albumin level tests also performed because in hypercalcemia these are elevated. Bone scan, prospective computed tomography (CT) scan for neck, chest and magnetic resonance imaging (MRI) may help to determined whether the tumor has metastasized to the bone [95].

*2.4.8. Hypercalcemia levels*

Normal level of calcium in the blood ranges between 8.7 – 10.4 mg/ dl. Correct calcium level in the blood could be determined by using the following equation:

Corrected calcium (mg/ dl) = measured calcium + ([4- albumin (g/ dl)] × 0.8).

Serum calcium ranging between 10.5 – 12.0 mg/ dl indicates mild hypercalcemia.

Moderate hypercalcemia is being diagnosed when serum calcium is between 12.0 – ≤ 14.0 mg/ dl.

Severe hypercalcemia (hypercalcemia crisis) occurs when serum calcium is higher than 14.0 mg/ dl and is associated with acute signs and symptoms [87, 90-96].

*2.4.9. Signs and symptoms of hypercalcemia*

Since calcium has a wide range of physiological actions so it has a myriad of clinical effects on multi organs. On central nervous system (CNS), hypercalcemia will cause fatigue, depression, confusion, headache, difficulty in thinking and stupor. Cardiovascular system effects manifestation will range from abnormal electrocardiogram to arrhythmias. Gastrointestinal system signs will involve constipation, nausea and vomiting. Hypercalcemia will cause impaired kidney function and as a consequence will lead to decrease in the renal excretion of calcium and thus increase in the severity of hypercalcemia. Dehydration, bone pain and lost of appetite has also been observed. The hypercalcemia due to primary

hyperparathyroidism is usually mild or moderate and the patient will be asymptomatic or only suffer from minor clinical signs mentioned above. While hypercalcemia occurs as a result of breast cancer is usually acute or subacute and the calcium level will be highly elevated and many of the clinical signs mentioned above will be manifested. While mild hypercalcemic patients will be asymptomatic and hypercalcemia will be detected fortuitously during routine laboratory screening [83, 97-99].

*2.4.10. Hypercalcemia treatments and options*

There are different types of treatments used for hypercalcemic patients whereby some are often use for daily cases and some others used for emergency cases of hypercalcemia:

**1.** Bisphosphonates (Etidronate, Clodronate and Pamidronate):

**2.** Plicamycin (Mithramycin)

**3.** Calcitonin (Calcimar®)

**4.** Zoledronic acid (Zometa®)

**5.** Glucocorticoids (Prednisone)

While for emergency cases with calcium level exceeding 13 mg/ dl the following treatments are preferred:

**1.** Normal saline 200-400 ml/ hour I.V.

**2.** Furosemide (Lasix®) 200-400 ml/ hour [83, 86, 87, 97-99].

*2.4.11. Role of age and gender*

Hypercalcemia is usually seen in aged female patients more than male where the main characteristic is the presence of hypercalcemia without any symptoms. The main cause is either malignant disease or hyperparathyroidism [83, 86].

*2.4.12. Mechanisms of hypercalcemia occurrence with malignancy*

Mechanism of hypercalcemia incidence in solid cancer patients can be divided into two groups. In the first group, hypercalcemia may or may not be associated with bone metastasis and the main factor is the solid cancer itself since it will produce systematic circulating humoral factors which will ultimately cause loss of calcium from the bone i.e., bone resorption. Moreover these factors will lead to increase in calcium reabsorption from renal tubules. So this group is named as humoral hypercalcemia of malignancy (HHM) which include lung, ovarian, head and neck, pancreas and kidney cancer but the most frequent are the lung and head and neck cancers. The main factors produced by the cancer cells responsible for this situation are PTH, PTH-like factors, transforming growth factors, colony stimulating factors and leukocyte cytokines. In the second group, hypercalcemia is mainly caused or produced by extensive bone metastasis (i.e., extensive localized bone destruction) which include breast cancer. Breast cancer is considered as the highest and the most frequent solid cancer associated with hypercalcemia

caused by bone metastasis. This hypercalcemia is called local osteolytic hypercalcemia (LOH). The main difference is that in LOH, hypercalcemia is caused by localized bone destruction resulting from bone metastasis by the solid cancer, while in HHM the systematic humoral factor is the sole responsible factor and that hypercalcemia is unrelated to the extent of bone metastasis. In LOH, hypercalcemia is produced by direct effect of the solid cancer cells on the bone i.e., by acting like osteoclast cell producing acid protease (lysosomal enzymes) and collagens responsible for removing of mineral from bone and mainly lead to resorption of bone matrix and causing an increase in cAMP and inhibition of microtubule assembly by agents like colchicine. Resorption could also happened or take place independently of osteoclast cell activity. While for hematological cancers i.e., myeloma the main causes for hypercalcemia are increase bone resorption and glomerular filtration impairment. The main cause of hypercalcemia during lymphoma is bone resorption associated with increase in absorption of calcium from the gut [82, 86, 100].

*2.4.13. Relation of hypercalcemia with nausea and vomiting*

The main mechanism of hypercalcemia incidence in solid cancer is the metastasis of the cancer to the bone. Breast cancer which is the highest type of the LOH has shown to cause bone marrow destruction leading to hypercalcemia. Hypercalcemia will lead to many side effects mainly nausea and vomiting and there are studies indicating that hypercalcemia is one of the main risk factor for nausea and vomiting [16, 101].

**2.5. Neurotoxicity**

Neurotoxicity which induced by chemotherapy can occurs because of the direct or indirect effect and/ or damage that chemotherapy will cause to the central nervous system (CNS) or peripheral nervous system or any combination of these [102]. It is a critical matter to distinct between the two components of the nervous system. The CNS consists from the brain and the spinal cord. CNS mainly responsible for controlling neurological function of mental status, level of consciousness, motor power, sensory function, cerebral function and cranial nerve function. While for the peripheral nervous system it consists of peripheral nerves, this system mainly responsible for sensing pain, temperature and sensation [103].

This side effect i.e., neurological toxicity remain as one of the major critical side effect of chemotherapy treatment. Its clinical presentation varies significantly as a result of that it became very difficult to confirm the diagnosis [104].

*2.5.1. General signs and symptoms of neurotoxicity*

Symptoms associated with neurotoxicity may include cerebellar effects i.e., (tremor, loss of balance and fine motor movements), confusion, visual impairment, peripheral neuropathy, somnolence and auditory [102].

It has been found that neurotoxicity problems usually temporary i.e., resolving once treatment is completed, even so sometimes permanent neurological deficits may happened [102].

*2.5.2. Blood-brain barrier and it's role in protecting CNS*

Blood-brain barrier consider as a very efficient part of the nervous system that determine whether a chemotherapy agent is able to reach the nervous system or not. This barrier has the ability to block certain chemotherapy agents from entering nervous system at the cellular level [105]. Blood-brain barrier which surrounding the CNS varies from the one which surrounding the peripheral nervous system, as a result of this variation some chemotherapy agents such as vincristine significantly affect the peripheral nervous system but not the CNS. Chemotherapy agent will produce neurotoxic effects only if it has the ability to cross the blood-brain barrier [106].

*2.5.3. Neurotoxicity and chemotherapy*

Chemotherapy agents that significantly associated with neurotoxicity include the following: 1- Platinum compounds, 2- Taxanes, 3- Vinca alkaloid [104].

*2.5.4. Factors associated with the incidence of neurotoxicity*

There are many factors play role in the incidence of neurotoxicity but the most critical factors are the following::

**1.** Chemotherapy doses.

**2.** Route of chemotherapy administration [107].

*2.5.5. Other factors*

The incidence of neurotoxicity can be related to factors other than chemotherapy, these factors are:

**1.** Primary or secondary tumor deposits, which may involve the nervous system.

**2.** Metabolic or electrolyte imbalance which will leads to neurological disturbance.

**3.** Neurological deficits [108].

*2.5.6. Neurotoxicity evaluation and management*

Treatment used for neurotoxicity that caused by chemotherapy agents is limited. The focus of care should be on early recognition of neurotoxicity and careful monitoring of patients at high risk of toxicity [109]. There are various agents that either block the development and/ or incidence of neurotoxicity that caused by chemotherapy agents. Even so the mechanisms of action for these agents still mysterious [110]. Example for agent used as antidote for encephalopathy cause by ifosfamide is the methylene blue [111], besides that amifostine and adrenocorticotropic hormone analogues have also been found to be an effective neuroprotective agents. But farther investigation still required to clarifying the role of these agents in overcoming and/ or preventing neurotoxicity problem which leads to either delay in chemotherapy schedule, reduction in chemotherapy doses or substitution with an alternative agent [104].

### 2.6. Cardiotoxicity

The major function of the heart is to pump the blood to the whole body to supply body organs with adequate oxygen and nutrition they need. This process will happened by contracting muscular walls of the left ventricle [112]. There are various factors which can leads to cardiac injury in the cancer patients. This may happened as a result of either infiltration of metastases to infections and/ or because of chemotherapy toxicity [112].

#### *2.6.1. Major factors which cause cardiac damage in cancer patients*

a-Cardiac tumors, b-Bacterial infections, c-Chemotherapy induce toxicity, e-Radiation induce toxicity, f-Fungal and/ or viral infection [113, 114].

Chemotherapy effects will be classified into two types: acute and chronic effects.

#### *2.6.2. Acute toxic effect*

Acute cardiotoxicity caused by doxorubicin came from combination of factors which are: mitochondrial changes, cellular degeneration and a loss of myocardial fibrils. The incidence of cardiotoxicity will be either during or after doxorubicin administration, this cardiotoxicity will leads to cardiac abnormalities which include: ST and T wave changes, sinus tachycardia, atrial and ventricular ectopics, complete heart block, supraventricular tachycardia and ventricular tachycardia [116, 117].

Although doxorubicin cause cardiotoxicity there is no specific treatment for this condition, but there is only a supportive treatments. Researchers and clinicians keep on using of cardioprotective agents that allow chemotherapy agents specifically anthracycline to be used at a higher dose without causing cardiotoxicity [114]. Example for these cardioprotective agents are dexrazoxane and amifostine [118].

#### *2.6.3. Chronic toxicity*

This type of toxicity is one of the most common toxicity caused by doxorubicin it is characterized by chronic dilated cardiomyopathy. This condition i.e., cardiomyopathy usually happened either at late of chemotherapy cycle or shortly after the end of it [119]. Cardiomyopathy is significantly attenuated by the chelation of iron. Moreover, cardiomyopathy has been diagnosed among the survivors of cancer patients who have been treated with doxorubicin during their childhood [120].

### 2.7. Pulmonary toxicity

It is one of the main side effects of chemotherapy, which become clinically obvious after weeks, months or even years of termination of chemotherapy. It usually associated with several clinical symptoms which are: dry cough, dyspnoea and progressive worsening of symptoms with a poor prognosis for recovery [121].

*2.7.1. Chemotherapy and pulmonary toxicity*

Chemotherapeutic agents will be divided into three groups, this will mainly based on their effects on pulmonary function:

1. Hypersensitive pulmonary reaction: Bleomycin, 6-mercaptopurine, methotrexate, mitomycin and procarbazine. This condition take place as a result of either desquamative interstitial pneumonitis or an eosinophilic pneumonitis [122, 123].
2. Non-cardiogenic pulmonary oedema: Cyclophosphamide, cytarabine and methotrexate. This condition will take place after few days of strating using of chemotherapy treatment.
3. Chronic pulmonary fibrosis: Bleomycin, busulfan, carmustine, cyclophosphamide, fludarabine, ifosfamide, methotrexate and mitomycin [122, 123]. This clinical condition will take place within months of using chemotherapy treatment.

Besides that it has been found that when mitomycin used in combination with vinca alkaloids and/or gemcitabine with docetaxel or when the later two agents i.e., gemcitabine and docetaxel used alone they can cause pulmonary toxicity [124, 125, 126, 127].

*2.7.2. Assessment of pulmonary function*

It is very important to assess patients pulmonary function before start administration of chemotherapy, the assessment will include the following:1- Chest X-ray 2- Lung biopsy required to differentiate chronic fibrosis from lung metastasis [121].

*2.7.3. Treatments used for pulmonary toxicity cases*

Managements used for pulmonary problems i.e., toxicity will include the following: 1- Bronchodilator, 2- Corticosteroid 3- Expectorant 4- Oxygen 5- Antibiotics 6- Nebulised saline 7- Aminophylline and theophylline [128-129].

## 3. Conclusion

Cancer has become a major killer in the world which almost surpasses the cardiovascular diseases and will become the main lethal cause in this century. Although the global war against cancer leads to remarkable gain in understanding the main molecular mechanism for the cancer cell, this progress is still consider as slow and not enough especially in case of treatment of common solid tumor in adults. Besides that there are so many types of serious side effects caused by the tumor itself or because of its chemotherapy treatment.

Therefore it is an obligate for all the clinicians and physicians to focus on these main side effects that emerged as a result of cancer itself or its treatment and working to built and develop treatment guidelines to overcome or palliate these major side effects.

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