ASSESSMENT OF CHEMOTHERAPY OUTCOME AND ADVERSE EVENT MANAGEMENT AMONG SOLID CANCER PATIENTS OF PENANG HOSPITAL

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ASSESSMENT OF CHEMOTHERAPY OUTCOME AND ADVERSE EVENT MANAGEMENT AMONG SOLID CANCER PATIENTS OF PENANG HOSPITAL

By

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DEDICATION

To

My great family specifically to my lovely father Abdul Rasool and mother Basma.

My darling wife Hiba and my sweet heart daughter Shams.

My great Brothers Rafid and Bilal.

(May Great ALLAH Bless My Soul)

Bassam

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µg	Micro gram
µl	Microliter
dl	Deciliter
Kg	Kilogram
gm (g)	Gram
L	Litter
mg	Milligram
m^2	Square Meter
ml	Milliliter
U	Unit
1^{st} cycle	First Cycle
2^{nd} cycle	Second Cycle
3^{rd} cycle	Third cycle
4^{th} cycle	Fourth cycle
5^{th} cycle	Fifth cycle
6^{th} cycle	Sixth cycle
ACD	Anemia of Chronic Diseases
ADH	Antidiuretic Hormone
ANS	Autonomic Nervous System
aPTT	Thromboplastin Time
ASCO	American Society of Clinical Oncology
ASHP	American Society of Health-System Pharmacist
ATP	Adenosine Triphosphate

CAF	Cyclophosphamide, Adriamycin and 5-Flurouracil
cAMP	Cyclic Adenosine Monophosphate
CBC	Complete Blood Count
cDNA	Cyclic Deoxyribonucleic Acid
CEF or FEC	Cyclophosphamide + Epirubicin + 5-Flourouracil
CFU-E	Colony Forming Unit-Erythroid
CINV	Chemotherapy Induce Nausea and Vomiting
CMV	Cytomegalovirus
CNS	Central Nervous System
CMF	Cyclophosphamide + Methotrexate + 5-Flourouracil
CRC	Clinical Research Centre
CT	Computed Tomography
CTZ	Chemoreceptor Trigger Zone
CYP	Cytochrome P450 Enzymes
DNA	Deoxyribonucleic Acid
D2	Dopamine-2 Receptor
ECAS	European Cancer Anaemia Survey
ESA	Erythropoiesis-Stimulating Agents
EPO	Erythropoietin
ESR	Erythrocyte Sedimentation Rate
FAO	Food and Agriculture Organization
FDA	United State Federal and Drug Administration (FDA)
FLIE	Functional Living Index- Emesis (FLIE) Questionnaire
GIT	Gastrointestinal Tract
Hb	Hemoglobin
HC	Hypercalcemia

Hct	Hematocrit
HEC	Highly Emetogenic Chemotherapy
HHM	Humoral Hypercalcemia of Malignancy
HIT	Heparin Induced Thrombocytopenia
HPE	Histopathological Examination
IDA	Iron Deficiency Anemia
IDIS	Medline and Iowa Drug Information Services
IMR	Institute for Medical Research
INF-γ	Interferon
IHM	Institute for Health Management
IHBR	Institute for Health Behavioral Research
IHSR	Institute for Health Systems Research
IPH	Institute of Public Health
ITP	Idiopathic Thrombocytopenic Purpura
I.V.	Intravenous
LOH	Local Osteolytic Hypercalcemia
MASCC	Multinational Association of Supportive Care in Cancer
MANE	The Morrow Assessment of Nausea and Emesis
MCV	Mean Corpuscular Volume
MEC	Moderately Emetogenic Chemotherapy
Meg-CFC	Megakaryocyte Colony Forming Cells
MOH	Ministry of Health of Malaysia
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NIH	National Institutes of Health
NICE	National Institute for Clinical Excellence

NK-1	Neurokinin Receptors
ONEM	The Osoba Nausea and Emesis
PO or p.o.	Per Oral
PONV	Postoperative Nausea and Vomiting
PS	Power and Sample Size Program
PT	Prothrombin Time
PTH	Parathyroid Hormone
PTHrP	Parathyroid Hormone-Related Protein
QOL	Quality Of Life
RBC	Red Blood Cells
rhIL-11	Recombinant Human Interleukin-11
rhTPO	Recombinant Human Thrombopoietin
rHuEPO	Recombinant Erythropoietin
RNA	Ribonucleic Acid
r_s	Spearman Correlation coefficient ()
SCF	Stem Cell Factor
SCC	Squamous Cell Carcinoma
SCCOHT	Small Cell Carcinoma of The Ovary and Hypercalcemic Type
TB	Tuberculosis
TNF-α	Tumor Necrosis Factor
TPO	Thrombopoietin
TT	Thrombin Time
TTP	Thrombotic Thrombocytopenic Purpura
UNICEF	United Nations International Children's Emergency Fund
USA	United State of America
USM	Universiti Sains Malaysia

VC	Vomiting Center
WBC	White Blood Cell
WHO	World Health Organization

PENILAIAN HASIL KEMOTERAPI DAN PENGURUSAN PERISTIWA ADVERS DI KALANGAN PESAKIT KANSER PEPEJAL HOSPITAL PULAU PINANG

ABSTRAK

Dalam abad ini, kanser telah menjadi salah satu masalah dan penyakit utama yang telah menyebabkan banyak kematian dan akan melebehi penyakit jantung. Penyakit kanser dan rawatan kemoterapi mempunyai banyak kesan sampingan yang berbahaya yang boleh menjejaskan kualiti hidup (QOL) pesakit-pesakit kanser.

Oleh itu kajian ini dilakukan untuk mengesan faktor-faktor risiko utama berkaitan dengan loya dan muntah, anemia, trombositopenia dan hiperkalsemia dan untuk menilai keberkesanan garis panduan rawatan masing-masing. Di samping itu QOL pesakit kanser payudara yang mengalami loya dan muntah juga dinilai. Kajian prospektif dan retrospektif telah dijalankan keatas pesakit-pesakit kanser pepejal yang dimasukkan ke Hospital Pulau Pinang. Data telah dikumpulkan dengan menggunakan kaedah temuduga secara bersemuka untuk bahagian prospektif (loya dan muntah-muntah) dan dengan menggunakan lembaran data khusus untuk bahagian retrospektif (anemia, trombositopenia dan hiperkalsemia). Maklumat telah dikumpul daripada fail-fail pesakit yang disimpan di klinik onkologi dan pejabat rekod hospital.

Kajian prospektif tertumpu terhadap faktor-faktor risiko dan QOL pesakit kanser payudara (n=158) yang mengalami loya dan muntah setelah rawatan kemoterapi. Faktor-faktor risiko ini termasuk data demografik pesakit, maklumat kanser payudara, data kemoterapi, data ciri-ciri pesakit dan rawatan loya dan muntah. Faktor-faktor utama berkaitan dengan loya dan muntah aruhan kemoterapi (CINV) tertangguh dan akut ialah etnik pesakit, kitaran dan jenis kemoterapi serta rawatan pra dan pasca antiemetik yang digunakan. CINV tertangguh mempunyai kesan negatif terhadap QOL pesakit kanser

payudara yang lebeh besar berbanding kesan CINV akut. Di samping itu, kajian menunjukkan bahawa terdapat kepincangan dalam garis panduan rawatan antiemetik yang mungkin disebabkan oleh perbezaan etnik dikalangan pelbagai bangsa.

Bahagian kedua adalah kajian retrospektif observasional ke atas pesakit kanser yang dimasukkan ke hospital di antara tahun 2003 dan 2009 yang mengalami anemia atau trombositopenia atau hiperkalsemia. Menurut kajian ini, faktor risiko utama berkaitan dengan anemia, trombositopenia dan hiperkalsemia adalah jenis dan tahap penyakit kanser; jenis kemoterapi; skedul kemoterapi, kitaran kemoterapi dan dos (tinggi) kemoterapi serta rawatan. Satu lagi hasil kajian penting yang diperolehi berkaitan dengan anemia (n=534 pesakit) ialah garis panduan rawatan yang digunakan adalah tidak cukup berkesan dan hanya bersifat sementara. Hasil kajian yang sama turut diperolehi untuk trombositopenia (n=341 pesakit) dan hiperkalsemia (n=292 pesakit), menunjukkan garis panduan rawatan tidak berkesan. Oleh yang demikian, garis panduan rawatan dan cadangan-cadangan baru digubal berdasarkan daripada hasil kajian ini.

Katakunci: Loya dan Muntah, Loya dan Muntah Tertangguh, Loya dan Muntah Akut, QOL, Anemia, Trombositopenia, Hiperkalsemia, Garis Panduan Rawatan.

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ABSTRACT

During this century, cancer has become one of the major problem and diseases which has caused predominant death and will even surpass heart diseases. Both cancer diseases and chemotherapy have many hazardous side effects which could also affect the quality of life (QOL) of cancer patients.

Thus this study was performed to detect the main risk factors associated with nausea and vomiting, anemia, thrombocytopenia and hypercalcemia and to evaluate effectiveness of respective treatment guidelines. In addition QOL of breast cancer patients with nausea and vomiting was also evaluated. Prospective and retrospective studies were conducted on solid cancer patients admitted to Penang, Hospital. Data were collected by using direct person-to-person interview for the prospective part (nausea and vomiting) and by using specific data sheet for the retrospective part (anemia, thrombocytopenia and hypercalcemia). The required data were collected from patients' files kept in the oncology clinic and the record office of the hospital.

The prospective study focused on risk factors and QOL of breast cancer patients (n=158) suffering from nausea and vomiting after chemotherapy administration. These risk factors include patient's demographic data, breast cancer information, chemotherapy data, patients' characteristic data and treatment of nausea and vomiting. The main risk factors associated with delayed and acute chemotherapy induced nausea and vomiting (CINV) are patients ethnicity, chemotherapy cycles and types, as well as pre and post antiemetic treatments used. As for the effect on QOL, delayed CINV has a higher negative effect on breast cancer patients QOL than acute CINV. Moreover it shows that there is a defect in the antiemetic treatment guideline which might be due to ethnic variation among the different races.

The second part is an observational retrospective study among solid cancer patients admitted between 2003 and 2009 who developed anemia or thrombocytopenia or hypercalcemia. According to this study, the main risk factors associated with anemia, thrombocytopenia and hypercalcemia are types and stages of solid cancer disease, chemotherapy type, chemotherapy schedule, chemotherapy cycle, and chemotherapy dose (high) as well as the treatment. Other important result related to anemia (n=534 patients) is that the treatment guidelines employed is not effective enough and was only temporary. Similar findings were obtained with thrombocytopenia (n= 341 patients) and hypercalcemia (n= 292 patients), indicating ineffectiveness of treatment guideline. Thus new treatment guidelines and recommendations are developed based on the findings.

Keywords: Nausea and Vomiting, Acute Nausea and Vomiting , Delayed Nausea and Vomiting, QOL, Anemia, Thrombocytopenia, Hypercalcemia, Treatment Guidelines.

CHAPTER 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. Cancer does not represents only one disease but it is a group involving about 100 diseases. Cancer is characterized by two things. Firstly there is no control for the growth of cancer cells and secondly is the ability of the cancer cells to metastasis and migrate from the original site to different parts of the body. There are two types of tumors which are malignant and benign cancer. Cancer can attack any person and its occurrence increases as the age of the individual increase too (Carson-De Witt, 2002; Markman, 2002). There are many problems (i.e., side effects) associated with cancer diseases either solid or hematological cancer 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 considered as one of the major diseases that will effect the quality of life (Dolan, 2005; Henry, 2005; Sitamvaram, 2005; Stephens, 2005).

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 killing the cancer cells which are characterized by their high multiplication and growth rate. It will also kill all the cancer cells that had broken off from the main tumor and spread to the blood or lymphatic system or any part of the body. This killing process of cells is either by a direct effect on deoxyribonucleic acid (DNA) or an effect on the factors involved in mitosis by inhibition of its synthesis or production or uses (Weir-Hughes, 2005; Scurr *et al*., 2005; Kelland, 2005). Chemotherapy drug may lead to complete cure for some types of cancers or may suppress the growth of others or may prevent their spread to other parts of the body. So many types of new therapies have emerged over the past 20 years. Some of them were straight forward, effective and safe and some have many side effects. 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 (Weir-Hughes, 2005; Rizzo and Closs, 2002).

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 (Abrams, 2001; Koda-Kimble *et al*., 2002; Rizzo and Cloos, 2002). 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 (Abrams, 2001; Koda-Kimble *et al*., 2002; Rizzo and Cloos, 2002).

Occurrence of specific side effects will vary according to the chemotherapy used. The most common side effects experienced are nausea and vomiting, anemia, hair lost, bleeding, thrombocytopenia, hyperuricemia, bone marrow depression, alopecia and mucositis. So different parameters must be taken into consideration to prevent, reduce and overcome these side effects (Abrams, 2001; Koda-Kimble *et al*., 2002; Rizzo and Cloos, 2002).

1.4 Main Problems Caused by Solid Cancer Diseases and Chemotherapy

1.4.1 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 digested and undigested food through the mouth. Nausea and vomiting can arises from a different or wide spectrum of etiologies which are either directly associated to cancer disease itself or its treatment. According to the new ranking of chemotherapy side effects, nausea is the number one or the most disturbing side effect, followed by fatigue, neutropenia, anemia or thrombocytopenia, hair losing 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 (Haggert, 1999; Oberleitner, 2002; Coates *et al*., 1983; Lebourgeois *et al*., 1999; Morrow *et al*., 2005; Hesketh, 2005; Rudd and Andrews, 2005).

1.4.1.1 Causes of Nausea and Vomiting

There are several factors involved in the stimulation of nausea and vomiting and these factors included stress, pregnancy, motion sickness, migraine headache, cancer stages, radio therapy and chemotherapy.

The main focus of this part of the study will be on the factors causing nausea and vomiting related with solid cancers specifically breast cancer and chemotherapy. Nausea and vomiting is one of the major problems that is 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 is associated with chemotherapy and cancer diseases (Haggerty, 1999; Oberleitner, 2002; Mitchell and Schein, 1984; Bartlett and Koczwara, 2002).

1.4.1.2 Nausea and Vomiting in Solid Cancer Patients

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 (Molassiotis and Böjeson, 2006). 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 (Molassiotis and Böjeson, 2006). With regards to solid tumor burden, breast cancer causes nausea and vomiting especially at its advance stages is by metastasis to the abdomen (mainly stomach or liver) or central nervous system (CNS). So emphasis on the details of the effect of advance

stages of cancer on nausea and vomiting should be made which up to now was given only little attention (Molassiotis and Böjeson, 2006).

1.4.1.3 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 (Haggerty, 1999; Oberleitner, 2002; Mitchell and Schein, 1984; Bartlett and Koczwara, 2002; Navari, 2007). Nausea and vomiting associated with surgery, chemotherapeutic agents, radiotherapy and pregnancy are thought to be induced by stimulating the dopamine-2 (D2), acetylcholine, histamine, and serotonin-3 ($5\text{-}HT_3$) neuro-receptors involved in activating specific areas of the brain that coordinate the act of vomiting (Beckley, 2005). Also some studies have reported the involvement of neurokinin receptors (NK-1) especially in delayed emesis, while histamine and muscarinic receptors have lesser role in emesis associated with motion sickness (Hesketh *et al.*, 2003; Grunberg and Hesketh, 1993). 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 $5\text{-}HT_3$ receptors in the GIT which will send impulses to the CTZ and VC. This is illustrated in Figure 1.1.

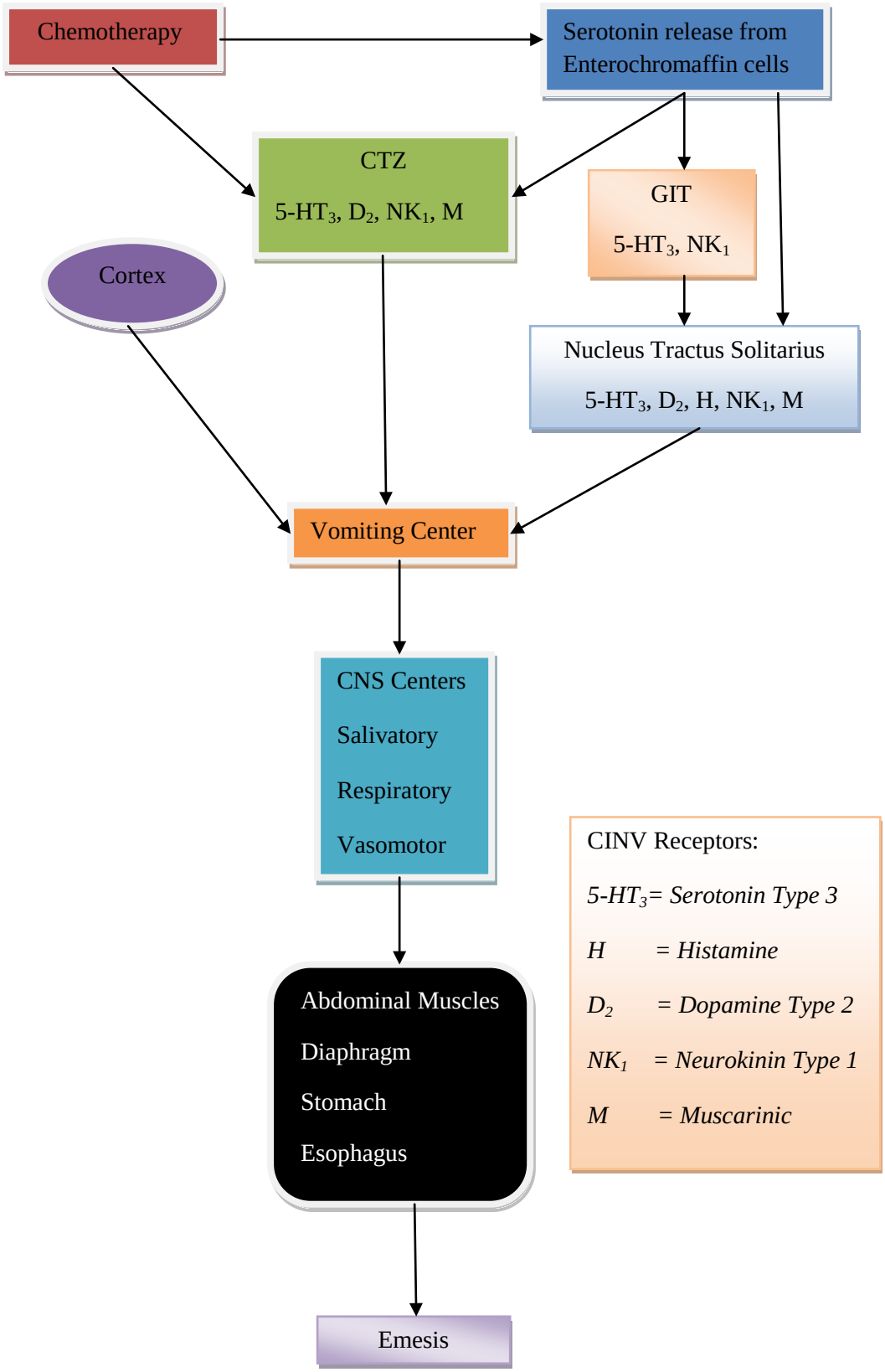

Figure 1.1 Responsible Neurotransmission Pathways for Chemotherapy Induce Nausea and Vomiting (CINV) (ASHP, 1999).

1.4.1.4 Major Patients Risk Factors Associated with Incidence and Severity of Nausea and Vomiting

Direct factors associated are: gender, age, history of motion sickness, history of vomiting during pregnancy, history of alcohol consumption and patient anxiety (Haggerty, 1999; Oberleitner, 2002; Hesketh, 2001; Osoba *et al*., 1997; Hesketh, 2005; Rubenstein, 2005).

When comparing between men and women, women have 2-3 fold higher chance of emesis or need for use of antiemetic prophylaxis treatment within the first 24 hours after receiving high dose of highly emetogenic chemotherapy. While in case of moderate emetogenic chemotherapy drugs, women have significantly lower response rate than men to 5-HT_3 antagonist either when it given as single or combination treatment with dexamethasone, for prevention or protection against emesis or freedom from nausea within the first 24 hours after chemotherapy administration. Other serious and important risk factor is the age, where by younger cancer patients are characterized by poor response to the antiemetic prophylaxis. When comparing the cancer patients according to their ages the results showed that higher percentage of the younger patients suffered from nausea and vomiting than older patients. In some studies the patients were grouped into those more than 55 years old and those less than 55 years old. In these studies the results showed that all patients more than the mean age of the study population showed lower risk of nausea and emesis with the chemotherapy. Also patients who suffered from nausea and vomiting of other etiologies are more susceptible to nausea and vomiting due to chemotherapy treatment. Emesis during pregnancy is consider as one of the risk factor for chemotherapy induce nausea and vomiting (CINV) but the evidence for it is still limited. Alcohol consumption has been indicated as one of protective factors against progress of CINV, however many factors are associated with alcohol consumption and thus this is still not clear whether heavy alcohol consumption (> 100 g/ day) is a protective factor itself or it will cause genetic change leading to protection from emesis. Some authors think that the chronic consumption of alcohol lead to lower sensitivity of chemoreceptor trigger zone to emetic stimuli (Hesketh, 2005). Patient anxiety is a predictive

factor for occurrence and development of delayed and anticipatory emesis. This is because anxiety stimulate the forebrain areas (cortex and limbic system) thus reduce the threshold which will make other inputs induce emesis easily (Hesketh, 2005).

1.4.1.5 Major Chemotherapy Factors Responsible For Incidence and Severity of Nausea and Vomiting

There are several chemotherapeutics factors that play 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 (Haggerty, 1999; Oberleitner, 2002; Hesketh, 2001; Hesketh, 2005; Ballatori and Roila, 2005).

According to the emetogenic potential, chemotherapy drugs are classified as severe, high, moderate, low and very low depending on the percentage of the cancer patients developing nausea and vomiting. Even with the low emetogenic potential chemotherapeutics drugs, there is still the chance of inducing nausea and vomiting when high doses are given. Another example whereby the emetogenic potential is affected by chemotherapy doses is with cisplatin. Cisplatin dose higher than 50mg/ m^2 will lead to 100% occurrence of emesis if antiemetic prophylaxis is not given. Cyclophosphamide is a moderate emetogenic drug when the dose used is between 500-750 mg/ m^2 but is a highly emetogenic drug when the dose is higher than 1500 mg/ m^2 (Haggerty, 1999; Oberleitner, 2002; Hesketh, 2001; Hesketh, 2005; Ballatori and Roila, 2005). Schedule of administration especially when various drugs are administrated together, will also lead to significant implications for clinical action and toxicity, which i.e., either increases or decreases toxicity or efficacy. This is because this schedule will have an effect on the pharmacokinetic, biochemical and cell related interactions example when cisplatin administration precedes paclitaxel, it will cause

antagonism in their action, while when sequence is inversed this will lead to synergistic effect and will lead to increase in the toxicity of the two drugs i.e., increases in their myelotoxicity, nausea and vomiting effect and other side effects. These are due to the pharmacokinetic interactions of both drugs (Haggerty, 1999; Oberleitner, 2002; Hesketh, 2001; Hesketh, 2005; Ballatori and Roila, 2005).

It is very important that there must be good control on emesis from the first cycle of the chemotherapy. This is because patients who experienced emesis with early stages of chemotherapy treatment will have poor response toward antiemetic treatments in the later cycles. Also response to the antiemetic prophylaxis will gradually decline over time with chemotherapy cycles and about 30% of the patients will develop emesis at the fourth cycle of chemotherapy. Rate of chemotherapy administration is another important factor related with incidence of emesis. This is seen with doxorubicin which is a moderate emetogenic agent, but became less emetogenic when given by continuous infusion and became highly emetogenic when given in more rapid rate of bolus dose (Haggerty, 1999; Oberleitner, 2002; Hesketh, 2001; Hesketh, 2005; Ballatori and Roila, 2005; Scurr *et al*., 2005).

1.4.1.6 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: Cisplatin I.V $\geq$ 50 mg/ m^2, Cyclophosphamide I.V > 1500 mg/ m^2 and Dacarbazine.
2- High (60%-90%) Example: Carboplatin, Cisplatin I.V < 50 mg/ m^2, Cyclophosphamide I.V 750 mg/ m^2 to 1500 mg/ m^2 and Cytarabine I.V > 1gm/ m^2.
3- Moderate (30%-60%) Example: Altretamine I.V PO dose, Asparginase, Cyclophosphamide (I.V) $\leq$ 750 mg/ m^2, Cyclophosphamide PO dose, Doxorubicin (I.V) 20 to 60 mg/ m^2, and Ifosfamide.
4- Low (10%-30%) Example: Capecitabine PO dose, Docetaxel, Doxorubicin liposomal, Fluorouracil and Gemcitabine.

5- Very low (less than 10%) Example: Bleomycin, Busulfan PO dose, Methotrexate < 50mg/ m^2 (Hesketh, 2000; Rubenstein, 2005).

1.4.1.7 Diagnosis of Incidence of Nausea and Vomiting

The diagnosis of nausea and vomiting is based on different parameters mainly severity, frequency of occurrence and duration of symptoms associated with nausea and vomiting (Haggerty, 1999; Oberleitner, 2002).

1.4.1.8 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 (Hesketh, 2005; KRIS *et al*., 1985; Haggerty, 1999; Oberleitner, 2002).

Acute emesis is defined as nausea and/ or vomiting or both that occurred within the first 24 hours after chemotherapy administration. It has very important characteristic which is the arbitrary time frame of 24 hours and according to this emesis most commonly occur within one to two hours. The peak of the emesis is within four to six hours and after which emesis will start to subside.

Delayed emesis include nausea and/ or vomiting happening after 24 hours of chemotherapy administration. Delayed emesis is best characterized by cisplatin administration whereby the emesis peaks within four to six hours and then subsides within the next 12 to 16 hours i.e., the acute phase. Then after 24 hours of quiescent period emesis will become obvious again, reaching its peak within 48 to 72 hours and this is the delayed phase. Usually this type of delayed emesis is less intensive than acute emesis and will

resolved in the next two to three days. Many chemotherapy other than cisplatin such as carboplatin, anthracyclines and cyclophosphamide can cause delayed emesis.

Anticipatory emesis happens in patients who already suffered from acute and delayed emesis during the previous cycles. There are many causes and factors which can cause anticipatory emesis prior to chemotherapy cycles. However if acute and delayed emesis are well controlled, anticipatory emesis within the next few years became a much less significant problem (Hesketh, 2005; Oberleitner, 2002).

1.4.1.9 Grading of Nausea and Vomiting Severity for Acute and Delayed Phase

Several numerical grading have been used to clarify the severity of nausea and vomiting as shown in Table 1.

Table 1.1: Grading of Chemotherapy Induced Nausea and Vomiting Severity for Both Acute and Delayed

Grade of severity	Grade 1	Grade 2	Grade 3	Grade 4	Grade5
Nausea	Loss of appetite without alter in eating habit	Oral intake decreases without significant weight loss, dehydration I.V fluids given < 24 hr	Inadequate oral fluids and calories intake, on I.V fluids, tube feeding or on TPN ≥24 hr	Life threatening consequences	Death
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hr; I.V fluids indicated < 24 hr	≥6 episodes in 24 h; IV fluids, or TPN indicated ≥24 h	Life-threatening consequences	Death

(Cancer therapy evaluation program VERSION 3.0, 2008).

1.4.1.10 Association of Acute Emesis with Delayed Emesis

Nausea and vomiting are not independent phenomena, they are both strictly correlated with each other in both acute and delayed phase. It has been found that delayed emesis is mainly dependent on acute episode so when emesis happens in the first cycle of chemotherapy administration (acute phase) then it will be absolutely observed in the delayed phase. Many studies have shown that patients with good protection against emesis during the first cycle of chemotherapy (acute phase) will show a low probability of delayed emesis with subsequent cycles (Ballatori and Roila, 2005). Incidence of delayed emesis is in the range of 50% to 90% in those patients who have poor control of emesis in their early chemotherapy cycles, as compare to about 10% to 50% in those who have good control of emesis in their early cycles (Rubenstein, 2005).

1.4.1.11 Nausea and Vomiting Treatment

The main goal of the antiemetic treatment is to abolish nausea and vomiting which in the last twenty years is consider as an inevitable chemotherapy side effects. This prevention is focused on the entire period of emetic risk which is 4 days for patients who received highly or moderately emetogenic chemotherapy (Navari, 2007; Jordan *et al*., 2005). 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 (Grunberg and Dugan, 2005). Modern antiemetic treatments help in preventing 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 (Grunberg and Dugan, 2005). The different types of treatments are as follows:

1- Serotonin-receptor antagonists (*5-HT_3*)
2- Dopamine-2-receptor antagonists
3- Corticosteroids
4- Neurokinin-1-recptor antagonists
5- Cannabinoids

6- Benzodiazepines (Jordan *et al*., 2005).

1.4.1.11.1 Serotonin-Receptor Antagonists (*5-HT$_3$*)

These agents are one of the most effective antiemetic treatment for acute nausea and vomiting caused by chemotherapy, even for the acute nausea and vomiting resulting from highly emetogenic chemotherapy like cisplatin. They selectively block the 5-HT3 receptor in the periphery (visceral vagal afferent fiber) and in the brain (CTZ) (Jordan *et al*., 2005; Oberleitner, 2002; Haggerty, 1999). These agents have specific characteristics as described below:

1- The lowest effective dose should be used because high doses will lead to saturation of receptors and will not lead to any enhancement in the antiemetic activity.
2- Both oral and intravenous route will give similar action.
3- Single dose is as effective as multiply doses regimens.
4- The adverse effects of these agents are acceptable (Jordan *et al*., 2005).

The 5-HT$_3$ antagonist drugs most commonly used are dolasetron (Anzemet®), granisetron (Kytril®) and ondansetron (Zofran®). These three drugs are found to be similar in their effect and side effect. Both ondansetron and granisetron can prevent 50%-60% of the emesis caused by the highly emetogenic chemotherapy (i.e., cisplatin). The effective dose for this are dolasetron (I.V= 1.8 mg/ kg, oral= 100 mg, PO= 100 mg), ondansetron (I.V= 0.15 mg/ kg or 8-24 mg, PO= 12-24 mg) and granisetron (I.V= 0.01 mg/ kg or 1 mg, PO= 2mg) (Kris *et al*., 1985; De Mulder *et al*., 1990; Hesketh *et al*., 1996; Cubbedu *et al*., 1990; Navari *et al*., 1995; Howland and Mycek, 2006).

1.4.1.11.2 Dopamine-2- Receptor Antagonists

These agents were the main agents for antiemetic therapy from 1950s until 1980s. However, their efficacy as single agents is low compared with other agents. These agents produce their antiemetic effect through blocking of the dopamine receptors in the CTZ and

VC. This antiemetic class is divided into butyrophenones (e.g., droperidol and haloperidol), phenothiazines (e.g., prochlorperazine) and substituted benzamides (e.g., metoclopramide). conventional dose of metoclopramide is effective in treating with emesis due to mild to moderate emetogenic chemotherapy. While in case of highly emetogenic chemotherapy like cisplatin, metoclopramide need to be given in high doses so it will produce its antiemetic effect by antagonism at the $5HT_3$ receptors. The high doses for metoclopramide is 1-2 mg/ kg which can be given for 6-8 times per day to a maximum dose of 12 mg/ day. The adverse effects especially when receiving high doses of these agents include orthostatic hypotension, extrapyramidal symptoms and sedation (ASHP, 1999; Kovac, 2000; Jordan *et al*., 2005; Ison and Peroutka, 1986).

1.4.1.11.3 Corticosteroids

Their mechanism of action as antiemetic is still unclear and not fully understood but are considered as safe and effective antiemetic. They exert their effect through prostaglandin antagonist or immunosuppressive effect. They act as a booster when use in combination with other antiemetic agents (e.g., metoclopramide and ondansetron) by increasing the emetic threshold. Dexamethasone has been vastly investigated and used for treatment of acute emesis. A dose of 8mg will be effective for moderately emetogenic chemotherapy and 20 mg is required for severely emetogenic chemotherapy (MASCC, 2004; The Italian Group for Antiemetic Research, 1998; The Italian Group for Antiemetic Research, 2004; Hesketh *et al*., 1994; Kovac, 2003; Jordan *et al*., 2005).

1.4.1.11.4 Neurokinin-1-Receptor Antagonists

They represent a new class of antiemetic agents. Aprepitant penetrate through blood brain barrier and selectively block the NK-1 receptor. It has been approved by United State Federal and Drug Administration (FDA) as an effective oral antiemetic drug which is very effective in preventing acute and delayed emesis due to high emetogenic chemotherapy (e.g., cisplatin or cisplatin base therapy). Several studies had proven that aprepitant augmented the

action of dexamethasone and 5-HT_3 combination in inhibiting acute and delayed emesis but specifically delayed emesis of highly emetogenic chemotherapy drugs. While for moderate emetogenic chemotherapy many studies showed that triple combination of aprepitant + dexamethasone + 5-HT_3 receptor antagonist show superiority in the first 24 hours followed by aprepitant for the next 2 days alone. MASCC and NCCN guidelines both indicated the effectiveness of aprepitant plus 5-HT_3 plus dexamethasone for the treatment of moderate chemotherapeutics drugs. The appropriate doses of aprepitant with acceptable side effects are 125 mg orally (p.o.) on day one and 80 mg (p.o.) on day 2 and 3. Since aprepitant is metabolized by CYP3A4 then dexamethasone dose must be reduced to about 50% when aprepitant is co administered in order to overcome any drug interaction (Jordan *et al*., 2005; Poli-Bigelli *et al*., 2003; Herrstedt, 2005).

1.4.1.11.5 Cannabinoids

The usefulness of cannabinoids is limited because of their major toxic effects like dizziness, hallucination and dysphoria. Dysphoria specifically happens among older cancer patients who actually represent the largest proportion of cancer patients. These agents produce their antiemetic effect by acting directly on cannabinoids receptors found in the brain stem. Even so these agents are considered slightly better effective than conventional antiemetics agents such as metoclopramide, haloperidol and clopramide. These agents are more useful to be used in younger patients rather than in older cancer patients because they cause less euphoric and dysphoric side effects. Doses in the range of 5-10 mg/ m^2, every 3-4 hours orally will give the useful effect (Frytak *et al*., 1979; Jordan *et al*., 2005; Grunberg and Dugan, 2005; Mannix, 2004).

1.4.1.11.6 Benzodiazepines

They are usually used as an addition to antiemetic treatment to reduce anxiety due to chemotherapy treatment and the risk of anticipatory nausea and vomiting. Lorazepam is the preferred for anticipatory nausea and vomiting. Its anti-anxiety and sedative effect is very

useful when added to combination of antiemetic treatments, but its use as a single antiemetic is limited. Dose for Lorazepam usually is 1 to 2 mg every 6 hours for I.V. and 1 to 2 mg every 6 hours for oral administration (Jordan *et al*., 2005; Kris *et al*., 1985; Kris *et al*., 1987).

1.4.1.12 Antiemetic guidelines for Acute and Delayed Chemotherapy Induced Nausea and Vomiting

The main guidelines used for the treatment of acute and delayed nausea and vomiting is shown in Table 2 below.

Table 1.2: Antiemetic Guideline for Acute and Delayed Nausea and Vomiting

Degree of Emetogenicity	Acute Emesis (Day 1)	Delayed Emesis (days 2-5)
High	Dex+NK1+5-HT_3	Dex+NK1
Moderate	Dex+NK1+5-HT_3 or Dex+5-HT_3	Dex alone or 5-HT_3 alone or metoclopramide alone or Dex+NK1
Low	Dex	Non
Minimal	Non	Non

5-HT_3= 5-HT_3 receptor antagonist, Dex= dexamethasone, NK1= neurokinin receptor antagonist(MASCC, 2004; Grunberg and Dugan, 2005; Morrow, 1985).

1.4.1.13 Nausea and Vomiting in Breast Cancer

Breast cancer is considered as the most common type of cancer among women and is the highest type of cancer in United Kingdom. It comprised 30.4% of all the cases of cancer occurrence in Malaysia in 2002. It was reported that 200,000 new cases were diagnosed in each year and about 46,000 women die because of breast cancer in United State of America (USA) each year (Chang and Lo, 2003; Jones *et al*., 2007; Rhodes and McDaniel, 2001; Brookes *et al*., 2007).

Metastasis is one of the main characteristic of breast cancer in advanced stages. About 50% of the cases have the ability to metastasis to different organs mainly to liver, stomach, colon, lung, brain, small bowel and skeleton. Metastasis to the stomach and brain may occur after several years from the first chemotherapeutic treatment i.e., when the breast cancer became the advanced stage (between 2 to 5 years following its diagnosis). The metastasis to the brain will cause several problems and the most important are gut disturbance, headache, seizure, nausea and vomiting. While the metastasis of the advanced breast cancer to the stomach will lead to the incidence of stomach cancer which could then lead to several gastrointestinal problems such as delay in gastric emptying and bowel obstruction. All these effects lead to nausea and vomiting (Chang and Lo, 2003; Jones *et al*., 2007; Rhodes and McDaniel, 2001; Brookes *et al*., 2007). About 60 to 75% of patients who have advanced stages of breast cancer also suffer from bone metastasis leading to incidence of hypercalcemia which would cause nausea and vomiting (Lipton, 2003).

Most of the chemotherapeutics agents used for treatment of breast cancer have an emetogenic potential that ranged between low (e.g., 5-flurouracil and gemcitabine) to moderate (e.g., cyclophosphamide and anthracyclines). Despite the physician having several effective and adequate antiemetic agents (5-HT_3 and NK-1 receptors antagonists) in preventing nausea and vomiting, nevertheless significant proportion of breast cancer patients still suffer from nausea and vomiting after chemotherapy (Booth *et al*., 2007; Choi *et al*., 2005; O' Shaughnessy, 2003; Hesketh, 2005). There are so many studies which focused on nausea and vomiting but very few of them are prospective observational studies in breast cancer exclusively that looked for the main risk factors associated with nausea and vomiting (Hesketh, 2005; Osoba, 2005).

Besides that, there are many studies looking at the effect of nausea and vomiting associated with chemotherapy use on patients quality of life but there are few if any that investigated the effect of nausea and vomiting associated with solid cancer stages on patients quality of life (Hesketh, 2005; Rhodes and McDaniel, 2001). Choi *et al.* (2005) indicated that the

adjuvant chemotherapy {cyclophosphamide + methotrexate + 5-flourouracil (CMF) and cyclophosphamide + epirubicin + 5-flourouracil (CEF)} used for breast cancer patients caused nausea and vomiting. Anthracyclines is one of the most common agents used for breast cancer treatment but their clinical uses are limited due to acute nausea and vomiting, alopecia, neutropenia, anemia and thrombocytopenia. So many of these breast cancer patients showed severe nausea and vomiting which lead to a decrease in about 50% of the chemotherapy doses especially those who were treated with cyclophosphamide + methotrexate + 5- fluorouracil (CMF). Also due to the nausea and vomiting a high percentage of the breast cancer patients contemplate of stopping the chemotherapy (Booth *et al*., 2007; Choi *et al*., 2005; O' Shaughnessy, 2003; Hesketh, 2005).

1.4.1.14 Ethnic Variation Role in 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 (Gross *et al*., 1999; Ruzilawati *et al*., 2007). Much of this distinction has shown to be caused by alteration of the human cytochrome P450 enzymes (CYP) (Ruzilawati *et al*., 2007). 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 (Ruzilawati *et al*., 2007). The CYP3A subfamily consists of 4 members: CYP3A4, CYP3A5, CYP3A7 and CYP3A47 and represents about 30% of the total CYP in the human liver. The most superior subfamily among the 4 types that play the major role in metabolism of more than 60% of all drugs used in human is CYP3A4 (Ruzilawati *et al*., 2007). Miscellaneous CYP3A4 alleles in the population may partake in interindividual variability in CYP3A4 activity (Ruzilawati *et al*., 2007). In case of cancer patients nausea and vomiting can be clinically significant and severely incapacitating side effects of cytotoxic

chemotherapy (Aapro, 2004). These symptoms can symbolize a major therapeutic challenge and if unsatisfactorily controlled by antiemetic treatment, will limit a patient's ability or desire to eat and drink, considerably reduce quality of life, threaten the success of therapy, and result in increased mortality, morbidity, and prominently health care costs (Aapro, 2004). The management of nausea and vomiting has enhanced greatly in recent years, with the utilization of 5-HT3 (serotonin3)-receptor antagonists (Bloechl-Daum *et al*., 2006). These agents in combination with corticosteroids have been instrumental in improving the control of vomiting among patients receiving chemotherapy (Bloechl-Daum *et al*., 2006). All 5-HT3 receptor antagonists are metabolized by the cytochrome P-450 enzymes: tropisetron and dolasetron predominantly by CYP2D6, ondansetron partially by CYP2D6 but also by CYP3A4, CYP2E1, or CYP1A2, and granisetron mainly by CYP3A4 (Kaiser *et al*., 2002). Even so there is significant percentage of cancer patients who do not respond well to 5-HT3 receptor antagonists. The most important cause for such individual variation in drug response may be differentiation in drug biotransformation by genetically polymorphic enzymes, such as the hepatic cytochrome P-450 enzyme subfamily (Kaiser *et al*., 2002).

Granisetron is an influential and highly selective 5-HT3- receptor antagonist that has little or no attraction for other 5-HT receptors, or dopaminergic, adrenergic, benzodiazepine, histaminic, or opioid receptors. In contrast, other 5-HT3- receptor antagonists have affinities for divers receptor-binding sites (Bloechl-Daum *et al*., 2006). For example, ondansetron has obvious binding to 5-HT1B, 5-HT1C and μ-opioid receptor sites. Although not proven, the binding of these agents to extra receptor subtypes other than their target receptor may lie beneath the inferior adverse-event profile seen with ondansetron compared with granisetron (Bloechl-Daum *et al*., 2006).

1.4.1.15 Literature Review for Nausea and Vomiting

Warr mentioned in his study that both nausea and vomiting are the major problems that more than half of the cancer patients population will suffer from, either by the effect of cancer disease itself or chemotherapy. He mentioned that because of the closeness between nausea and vomiting many of the cancer patients express them as one symptom. Also Warr mentioned that some times one symptom will occur or take place without the other like for mild to moderate nausea it will not be accompanied by retching or vomiting. While patients with brain metastases and esophageal obstruction suffer from vomiting without preceding nausea. Warr showed that the physiology of nausea is still not clear and thus the prevention of vomiting is much easier than nausea. In his study he mentioned that nausea and vomiting occur in cancer patients either because of the cancer itself or because of the chemotherapy. But when cancer is the main cause this will required many investigations such as careful history, laboratory tests and physical examination in order to determine the underlining causes for nausea and vomiting with cancer so as to treat them correctly. Before 1980s a very high percentage of cancer patients treated with cisplatin or doxorubicin suffered from nausea and vomiting but the discovery and use of 5-HT_3 receptor antagonist with corticosteroids in 1990, had somewhat solved and prevent the occurrence of nausea and vomiting. However till now nausea and vomiting is still considered as a serious problem (Warr, 2008).

While Antonarakis and Hain (2004) described the effect of the chemotherapeutics drugs on the body cells is very harsh and thus the body will expel them as soon as possible by inducing nausea and vomiting. They also described nausea and vomiting as the most intractable, unpleasant and disgusting side effect suffered by many cancer patients especially children. Thus this emphasized that there are many risk factors related with patients that play a major role in nausea and vomiting incidence and severity including being female, young age, anxiety, motion sickness and poor control with previous chemotherapy. They also reported that risk factors responsible for nausea and vomiting incidence and severity associated with chemotherapy itself, route of administration, schedule and rate of

administration and the most important factor is the intrinsic emetogenicity factor of the chemotherapy itself. Thus the chemotherapy drugs are classified according to their emetogenicity.

Jordan *et al*. (2005) discussed the use of 5-HT_3 and dexamethasone and considered that their use since 1990s has lead to the control of acute (70%) and of delayed emesis (40%) among cancer patients treated with highly emetogenic chemotherapy. She and her colleagues also reported that NK1 receptor antagonist offered a very effective protection against nausea and vomiting especially the delayed phase. Apart from NK1 others antiemetic drugs are also available for protection against emesis.

It has been notice that there is a strong association between gender and occurrence of nausea and vomiting as gender is one of the risk factor for onset of both symptoms. Thus it has been reported that female is less responsive to antiemetic treatment than male and the main reason leading to the reduced antiemetic drug effect among female is the polymorphism of genes regulating the serotoninergic system. Another factor considered as a risk factor for nausea and vomiting is race whereby it was reported that the incidence of nausea and vomiting associated with chemotherapy use among Asian cancer patients is much higher than those African and Caucasian cancer patients (Klosterhalfen *et al*., 2005).

Age also play a role in the incidence and severity of nausea and vomiting since it has been found that nausea and vomiting occurrence and severity is more among the younger patients as compared to the older patients (age > 50 years old). Other risk factors associated with incidence and severity of nausea and vomiting are prior history of nausea and vomiting with chemotherapy and alcohol consumption. The incidence and severity were reported to be more in patients with uncontrolled nausea and vomiting history and among patients who do not drink alcohol (Cancer care Nova Scotia, 2004/ www.cancercare.ns.ca/).

A pilot study by Grote *et al*. 2006 in 5 oncology centers in USA involving a total numbers of 58 cancer patients reported that 47% of them were women with breast cancer and

52% were treated with cyclophosphamide based chemotherapy. The main objective of their study was to evaluate the efficacy of 5-HT_3 receptor antagonist i.e., palonosetron plus dexamethasone and aprepitant. The main results of this pilot study were that the main response towards this antiemetic combination was great. The proportion of those with no vomiting during the acute phase (0-24 hours) was 88%, while for those with delayed response (> 24-120 hours) was 78%. Also reported that 90% of the patients have no vomiting during the whole time interval and between 57% to 71% of the patients did not vomit during the 5 days post chemotherapy period. There were also no nausea incidence. So the main conclusion Grote and his colleagues reached was that the combination of antiemetic treatment for the prevention of both nausea and vomiting of moderate chemotherapy treatment was good and effective.

Booth *et al*., (2007) made a prospective study on 143 breast cancer patients in Canada and reported that most of them (91%) suffered from early stages of breast cancer. The mean age of the patients was 51.4 years that ranged from 24 to 76 years. The patients received 766 cycles of chemotherapy (range 1-6 cycles; median= 3 cycles) and the main chemotherapy used was anthracyclines. Booth and his colleagues mentioned that the chemotherapy used in breast cancer treatment were either low emetogenic chemotherapy (taxanes, gemcitabine and 5-flourouracil) or moderate emetogenic chemotherapy (cyclophosphamide and anthracyclines). In the first 24 hours, very few patients (10%) showed severe (i.e., grade 4) nausea and vomiting, but in the delay phase 70% of the patients developed grade 1 - 3 nausea. Unlike most studies, this prospective study focused on all the 6 cycles of chemotherapy and reported that the prevalence of nausea and vomiting was insignificantly affected by multiply cycles of chemotherapy. The differences in the grades of nausea and vomiting either acute or delayed associated with chemotherapy happened within the first cycle. In their study it was also observed that very few patients suffered from severe nausea and vomiting (i.e., < 10%). This could be because most of the patients were at the early stage of breast cancer and were treated with anthracyclines chemotherapy which has moderate

emetogenic potential and also they were treated with an effective antiemetic treatment (NK-1 antagonist). The major symptom observed in this study was delayed nausea (70%) which emphasized the difficulty to control such symptom as compared to vomiting.

Bloechl-Daum *et al*. (2006) accomplished a prospective, multicenter and multinational study in Denmark on 298 cancer patients treated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). They suffered from different types of cancer but breast and lung cancer were the most common type. The main objective for this study was to determine the impact of CINV on patients QOL. Data collection process was done by using functional living index- emesis (FLIE) questionnaire. The main results of this study was that CINV continue to adversely effects cancer patients QOL, especially nausea which has a greater negative impact on QOL than vomiting. This study mentioned that it is very important to find or develop a new antiemetic regimen and suggested that studies should investigate and examine the effectiveness of new antiemetic guideline by ASCO in reducing or preventing the negative impact of CINV on cancer patients QOL.

Cohen *et al*. (2007) conducted a study in California, USA on 151 cancer patients. Fifty-five percent of them were breast cancer patients followed by patients with lymphoma, lung and other different types of cancer. The patients were from different races and ethnicity. The main objectives of their study were to determine the prevalence of acute and delayed nausea and vomiting caused by chemotherapy treatment and to evaluate their effect on patients. The data were collected from cancer patients who were scheduled for the first cycle of new chemotherapy regimen and the occurrence of CINV were recorded by completing a daily dairy and the Functional Living Index-Emesis (FLIE tool). The main result was that CINV has a direct effect on cancer patients QOL.

The main differences between these two studies and present study is that they were just looking for the negative impact of CINV on cancer patients QOL with different types of chemotherapy regimens and different types of cancer but did not look at the main risks factors for nausea and vomiting onset and severity which was performed in our study.

Besides that present study will also try to find the main impact of delayed CINV on breast cancer QOL. Also the FLIE questionnaire employed by the researchers only focused on the assessment of cancer patients QOL, but not related with the effectiveness of antiemetic treatments. While present study will be focusing on specific type of solid cancer, specific chemotherapy regimens, main risk factors for nausea and vomiting onset and severity, effectiveness of the antiemetic treatments and on the main impact of CINV i.e., acute and delay on cancer patients QOL. This present study also used a mix questionnaire of MANE and ONEM to look for the two main parameters which are the effectiveness of antiemetic treatment and the impact on QOL. According to the World Health Organization (WHO), the definitive goal for palliative care is the achievement of the best QOL for cancer patients which could be accomplish by distinguishing the main risk factors, proper treatment and symptoms (Beijer *et al*., 2008) which are the main emphasis of present study.

Glaus *et al*. (2004) also conducted a prospective cross-sectional study on 249 cancer patients from several centers in Spain, Germany, Austria and Switzerland. The main aim of their study was to evaluate the incidence of moderate to severe emetogenic chemotherapy induce nausea and vomiting and their effect on patients daily life activities. About 78% of the patients were women, with a mean age of 54 years old. Breast, lung and ovarian cancers were the most predominant cancer and each patient was treated with 2.0 types of chemotherapy agents and 2.5 types of antiemetic drugs. The main results were that delayed emesis was the highest in incidence (38%) as compared to acute emesis. Even in those patients treated with adequate antiemetic treatment delayed emesis incidence was still high. The main explanation given was patients were not treated optimally for delayed emesis or may be because they were treated with cyclophosphamide. Another explanation given was that the neurological control for delayed and acute emesis are distinctly different from each other, and therefore the main control of risk factor for delayed emesis incidence is still unclear.