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PHARMACEUTICAL CARE NEEDS FOR PATIENTS RECEIVED CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

NIBAL ABUNAHLAH

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CLINICAL PHARMACY DEPARTMENT

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II. ACKNOWLEDGEMENTS

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III. CONTENTS

IV. ABBREVIATIONS and SYMBOLS LIST

AGA: Adherence with Guidelines for Acute Prevention of Chemotherapy Induced Nausea and Vomiting

ALT: Alanine Aminotransferase

ALT: Alanine Aminotransferase

ANV: Anticipatory Nausea and Vomiting

ASCO: American Society for Clinical Oncology

AST: Aspartate Amino Transferase

AST: Aspartate Aminotransferase

CAM: Complementary and Alternative Medicine

CINV: Chemotherapy Induced Nausea and Vomiting

CrCL: Creatinine Clearance

CT: Chemotherapy

CTZ: Chemoreceptor Trigger Zone

DDIs: Drug – Drug interactions

ECG: Electrocardiogram

ECG: Electrocardiogram.

EORTC QLQC30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

ESMO: European Society for Medical Oncology

FDA: Food and Drug Administration

FLIC: Functional Living Index Cancer

FLIE: Functional Living Index Emesis

FU: Flurouracil

GAGA: Guideline adherence group for acute control of CINV

GAGD: Guideline adherence group for delayed control of CINV

GCCP: Guideline Consistent Cohort Group

GICP: Guideline Inconsistent Cohort Group

GNGA: Guideline nonadherence group for Acute control of CINV

GNGD: Guideline nonadherence group for delayed control of CINV

GTDs: Granisetron Transdermal Patches.

HEC: High Emetogenic Chemotherapy

HGB: Hemoglobin

HT_3: Hydroxytryptamine-3

IV: Intravenous

KKKB: Kemoterapi Kaynaklı Bulantı ve Kusma

LEC: Low Emetogenic Chemotherapy

LV: Leucovirin

MAO: Malignant Bowel Obstruction

MASCC: Multinational Association of supportive Care in Cancer

MEC: Moderate Emetogenic Chemotherapy

NCCN: National Comprehensive Cancer Network

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Effect.

NGA: Nonadherence with Guidelines for Acute Prevention of Chemotherapy Induced Nausea and Vomiting

NGD: Nonadherence with Guidelines for Delayed Prevention of Chemotherapy Induced Nausea and Vomiting

NGD: Nonadherence with Guidelines for Delayed Prevention of Chemotherapy Induced Nausea and Vomiting

NID: No Impact on Patients quality of life

NK1: Neurokinin 1 Receptors.

PCPP: Patient Centered Pharmacy Practice

PMR: Progressive Muscle Relaxation

PMRT: Progressive Muscle Relaxation Training

QOL: Quality of life

RCT: Randomized Control Trial.

RR: Relative Risk

SD: Systemic Desensitization.

SPSS: Statistical Package for the Social Sciences

THI: Tryptophan Hydroxylase Inhibitors

VAS: Visual Analog Scale

WBC: White Blood Cell

WHO: World Health Organization

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Pharmaceutical Care Needs for Patients Received Chemotherapy Induced Nausea and vomiting

Nibal Abunahlah; **Supervisor:** Assoc. Prof. Dr. Mesut Sancar; Clinical Pharmacy Department.

1. SUMMARY

Aim: To determine the pharmaceutical care needs for patients receiving antiemetic to treat chemotherapy induced nausea and vomiting.

Material and Method: 100 chemotherapy naive patients were included in the study during May to September 2015. The antiemetic prescribing patterns and the adherence with guidelines were assessed (MASCC/ESMO 2014). The patients were instructed to record the incidences of vomiting in a daily dairy and described their nausea using the seven items Likert Scale. The incidence of chemotherapy induced nausea and vomiting (CINV) was recorded from day one to day five. To assess the patient's quality of life, a Turkish modified version of the Functional Living Index-Emesis (FLIE) questionnaire was administered to patients before chemotherapy. and five days after receiving chemotherapy. A side effect record form was given to patients to be signed. Drug-drug interaction was checked using Medscape Multi-Drug Interaction Checker.

Results: Guidelines nonadherence was observed in acute and delayed prevention of CINV (20% vs 72%). Complete control was 100% in adherent and 70% in nonadherent in acute CINV ($p<0.001$); while it was 78.6%. 27.8% in adherent and no adherent prevention of delayed CINV; respectively ($p =0.005$). Nonadherence had quality of life score of 97.4, 97.2 while adherence had 104.1, 116.9 in acute and delayed prevention of CINV; respectively ($p<0.001$). Nonadherence was associated with a higher incidence of side effects. 61% of the population have drug interactions. Six patients didn't receive any patient education resulted in treatment failure.

Conclusion: The pharmaceutical care needs for management of CINV includes ensuring adherence to international guidelines, enhancing rational antiemetic use, drug–drug interaction monitoring and optimizing patient education.

Keywords: Chemotherapy induced nausea and vomiting, pharmaceutical care, clinical pharmacist, oncology, quality of life

Kemoterapi Kaynaklı Bulantı Kusma Tedavisi Alan Hastaların Farmasötik Bakım Gereksinimlerinin Saptanması

Nibal Abunahlah; **Danışman**: Doç. Dr. Mesut Sancar; Klinik Eczacılık Anabilim Dalı

2. ÖZET

Amaç: Kemoterapi kaynaklı bulantı ve kusma (KKBK) sorunu için antiemetik tedavi alan hastaların farmasötik bakım gereksinimlerini saptamaktır.

Gereç ve Yöntem: Çalışmaya ilk defa kemoterapi tedavisi alacak olan 100 hasta dahil edildi. Antiemetik ilaç reçeteleme şeklinin kılavuzlara uygunluğu MASCC/ESMO 2014 kriterlerine göre değerlendirildi. Hastalardan günlük kusma sıklıklarını not etmeleri ve bulantı şikayetlerini 7 basamaklı Likert Skalasına göre tanımlamaları istendi. KKBK 1. günden 5. güne kadar kayıt edildi. Hastaların yaşam kalitesini değerlendirmek için Türkçeye valide edilmiş Fonksiyonel Yaşam Indeksi-Kusma (FLIE) anketi kemoterapi öncesi ve kemoterapi aldıktan 5 gün sonra tüm hastalara uygulandı. Olası tüm yan etkileri içeren bir yan etki değerlendirme formu kullanıldı. Bu forma göre hastalar eğitilerek yan etkilerin varlığı ve derecesini kaydetmeleri istendi. Medscape Multi-Drug Interaction Cheker kullanılarak ilaç-ilaç etkileşimleri kontrol edilmiştir.

Bulgular: Akut ve gecikmiş dönem KKBK sorununu önlemede kılavuzlara uyumsuzluk oranları sırasıyla %20 ve %72 olarak saptandı. Akut KKBK sorunu olup kılavuza uyumlu olanlarda tam kontrol oranı %100 iken; kılavuza uyumlu olmayanlarda bu oran %70 olarak bulundu ($p<0.001$); aynı durum gecikmiş KKBK sorunu olanlarda sırasıyla %78.6 ve %27.8 olarak hesaplandı ($p =0.005$). Kılavuza uyumlu olmayanlarda yaşam kalitesi skorları akut ve gecikmiş KKBK için sırasıyla 97.4 ve 97.2 iken; kılavuza uyumlu olanlarda bu ortalamaların daha yüksek olduğu görüldü (sırasıyla 104.1 ve 116.9. $ps<0.001$). Kılavuza uyumsuzluk saptanan grupta yan etki oranları daha yüksek saptandı. Hastaların %61'inde ilaç etkileşimi mevcuttu. 6 hasta hiç bir şekilde eğitim almadığı için bu hastaların tedavilerinin başarısızlıkla sonuçlandığı gözlendi.

Sonuç: KKBK yönetimi için farmasötik bakım gereksinimleri şunları kapsamalıdır: Uluslararası kılavuzlara uyulduğundan emin olmak, antiemetik ilaçların akılcı kullanımını sağlamak, ilaç-ilaç etkileşimlerini izlemek ve hastan eğitimi kalitesini artırmak.

Anahtar Sözcükler: Kemoterapi kaynaklı bulantı-kusma, farmasötik bakım, klinik eczacı, onkoloji, yaşam kalitesi

3. INTRODUCTION and AIM

Chemotherapy-induced nausea and vomiting (CINV) is a disruptive and unpleasant side effect in chemotherapy patients and is associated with decreased adherence to effective chemotherapy regimens (Herrstedt, 2002). Aside from these clinical consequences; CINV has a considerable economic impact. The additional breakthrough medications and increased hospitalization need result in an incremental increase in total medical costs (Tina Shih, 2007). Work attendance and performance are negatively affected; patients with uncontrolled and controlled CINV have average work day losses of 6.23 and 3.61 days, respectively (Tina Shih, 2007). The negative impact of CINV on patient quality of life has been assessed in numerous studies reporting expeditious deterioration in quality of life scores in post chemotherapy (Lindley and Hirsch, 1992; Bloechl-Daum, 2006; Ballatori et al., 2007; Cohen et al., 2007; Fernandez-Ortega et al., 2012).

Over the past four years, the management of CINV has shown consequential advances and many effective antiemetic drugs have been introduced into the market. When used correctly, antiemetic drugs can prevent 70 to 80% of CINV (Jordan et al., 2014). The antiemetic guidelines make it easy for physicians to incorporate the most recent clinical information into daily practice. These guidelines summarize all the clinical data derived from a huge number of clinical trials into simple recommendations that can be utilized easily by physicians. The Multinational Association of Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO), the American Society for Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) all support these guidelines and make them easily accessible from their websites; however, physicians still neglect this evidence (Jordan et al., 2014).

The patient care is a systemic and extensive process. A direct interaction with the patients and health care providers to ensure consistent and optimum care for every patient seen. All the medical team share in this process but with different aims and goals. The primary aim for the pharmacist is to provide pharmaceutical care by identify, solve and prevent drug therapy problems (Schwinghammer, 2011).

Drug therapy problems include unnecessary drug therapy, wrong drug, inappropriate dose, adverse drug reaction, poor adherence and additional medication needs (McDonough et al., 2003).

In order to improve clinical outcomes in patients receiving chemotherapy, care should address the management of supportive therapy, especially control of chemotherapy side effects like CINV, in addition to individualized treatment depending on risk assessment. To develop a pharmaceutical care model for those patients, both an examination of patient's needs and an understanding of the implications for pharmaceutical care are required.

The aim of the study is to determine the pharmaceutical care needs for patients receiving antiemetic drugs to treat chemotherapy induced nausea and vomiting. To identify those needs the study has many objectives which include evaluation of the antiemetic regimens that routinely given to the patients and assess their suitability with the emetogenicity level of the chemotherapy, assess the adherence of antiemetic regimens with the international guidelines, determine the efficacy of antiemetic regimens in treatment of CINV, identify the potential adverse effects associated with the use of these regimens, evaluate the potential drug-drug interaction in these group of patients, assess the effect of the antiemetic treatment regimen on the patient's quality of life and determine other factors that may lead to decrease the efficacy or failure of antiemetic regimens.

4. GENERAL INFORMATION

This part of thesis includes general information about pharmaceutical care, cancer and its treatment options, definition of nausea, vomiting and retching and explanation of different phases, mechanism and types of CINV, risk factors. The impact of these side effect on the patient's quality of life and the possible strategies to control CINV will be additionally discussed.

4.1. Pharmaceutical Care

Pharmaceutical care is a comprehensive term that describes a patient centered pharmacy practice (PCPP). In PCPP the pharmacist works with patient and with other health care provider to achieve positive outcomes. These outcomes are cure of a disease; elimination or reduction of a patient's symptomatology; arresting or slowing of a disease process; or preventing a disease or symptomatology and optimize health related quality of life (Hepler and Strand, 1990).

Cancer patients are at high risk group and requires higher treatment cost where toxic medications and manageable side effects require intensive pharmaceutical care: optimization of the health related Quality of Life (QoL) optimization is one of the gold standard for pharmaceutical care. The accurate diagnosis and proper management of cancer have a major impact on every aspects of cancer patient's quality of life (Donovan et al, 1989).

Pharmaceutical care involves the process which a pharmacist cooperates with a patient and other professionals in designing, implementing and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient by identifying and resolving potential and actual drug-related problems, and preventing drug-related problems. Pharmacists have the greatest and a specific drug related knowledge among the health care team (Jaehde et al, 2008). Studies that conducted to assess the pharmaceutical care in cancer patients are infrequent (Bremberg et al., 2006; Ruder et al., 2011; Delaney et al., 2009; Lin et al., 2015; Chew et al., 2015). Although these studies have different methodology and conducted in different

countries, they share the same positive outcome of implementation pharmaceutical care in oncology patients.

4.2. Cancer Definition and Treatments

Cancer is a class of diseases characterized by out of control cell magnification. There are over 200 variants of cancer, and each is relegated by the type of cell that is initially affected (http://www.who.int/cancer/nccp/en/, Access date:18/3/2016) External factors such as tobacco, infectious organisms, chemicals and radiations and internal factors such as inherited mutations, hormones, immune conditions and mutations that occur from metabolism can cause cancer.

Cancer treatments programs aim to remedy or considerably protract the life of patients and to ascertain the best possible quality of life to cancer survivor (http://www.who.int/cancer/nccp/en/, Access date:18/3/2016). Prevention, early detection, treatments and palliative care are the main components of cancer control.

As cancer refers to a class of diseases, so it is unlikely that there will ever be a single treatment to remedy cancer, the possible strategies for cancer managements include surgery, chemotherapy, radiation therapy, hormonal therapy and targeted therapy (Immunotherapy) (http://www.who.int/cancer/treatment/en/, Access date: 18/3/2016).

Surgery is the oldest strategy; it is may be curable to some types of non hematological cancers unless there is metastasis to other sites of the body. Surgical procedure is additionally used for diagnosis and staging of the cancer. To diagnose cancer a surgeon may take biopsy, if the biopsy contains cancer cells it may show the type of cancer and how gradually or expeditiously it may grow. Astaging surgery is performed to define the size of the tumor whether it has spread (Rosenberg, 2008).

A radiation therapy uses high energy radiation to shrink tumors and kill cancer cells (Lawrence et al., 2008). X-rays, gamma rays and charged particles are types of radiation that utilized for cancer treatment. Radiation therapy may be distributed as external beam radiation or internal radiation therapy (brachytherapy). It can be given

with a curative intent alone or with surgery or chemotherapy, or with palliative intent to reduce symptoms or suffering caused by cancer (Lawrence et al., 2008).

Hormonal therapy is a systemic therapy that reduce hormone levels or block binding of hormone to cell receptor. Generally hormonal therapy is a well tolerated and have lower side effects than cytotoxic agents (Cassidy et al., 2010b).

Targeted therapy is a special type of chemotherapy that has the ability to distinct between normal cells and cancer cells. It is sometimes used alone, but most often used with other treatments such as chemotherapy, surgery, and/or radiation therapy. These drugs tend to have different (and often less severe) side effects than standard chemotherapy drugs (Cassidy et al., 2010a).

Chemotherapy agents are a systemic chemical drugs for cancer treatment, they are able to reach many components of the body. Therefore, they are recommended for cancer that has already spread to other areas of the body, for tumors that occur at more than one site, or for tumors that cannot be abstracted surgically. It is withal used when a patient has recurrent disease after initial treatment with surgery or radiation therapy (Corrie, 2008). For some cancers, chemotherapy alone can eradicate all the cancer cells and remedy the cancer (primary treatment). As an adjuvant treatment, chemotherapy is given prior to or after other methods to increment the efficacy of cancer treatment. Most often, adjuvant chemotherapy is given after other therapies that have eradicated the clinically detectable cancer cells. The purpose of adjuvant chemotherapy is to reduce the jeopardy of recurrence or to protract survival. If remedy is not possible, chemotherapy may be given to minimize the discomfort caused by cancer or slow the progression (palliative treatment) (Corrie, 2008). Chemotherapy agents have both positive and negative effect on patient's health related quality of life. Alleviating symptoms and slowing, halting or inverting deteriorations in functioning are the main goals of chemotherapy regimens, however their side effects are extremely offensive. Nausea and vomiting are earnest side effects of chemotherapy that can dramatically affect the patient's quality of life (Ballatori et al., 2007).

Major advances in the treatment of CINV, such as an introduction of 5-HT_3 and neurokinin-1(NK-1) antagonists have considerably reduced the incidence of chemotherapy-induced vomiting but nausea and anticipatory nausea and vomiting (ANV) remain main offensive side effects among cancer patients (Jordan, 2007; Lasseter et al., 2007; Mustian et al., 2008).

4.3. Definition of Nausea. Vomiting & Retching

4.3.1. Nausea

Nausea is a subjective, difficult to describe, sick or queasy sensation, usually perceived as being in the stomach that is sometimes followed by emesis. Nausea and emesis are not indispensably on a continuum. One can experience nausea without emesis and one can have sudden emesis without nausea (Stern et al., 2011).

4.3.2. Vomiting

Vomiting is an organized, autonomic response resulting in a rapid and forceful expulsion of gastric contents through the mouth (Williams and Cosgrove, 2012). It is a highly concrete physical events, which is customarily, but not always proceeded by nausea. The ability to vomit presumably conveys a survival advantage by enabling the explosion of toxins from the stomach (Glare et al., 2011).

4.3.3. Retching

In retching the patient try to vomit without expulsion of gastric content and described as “Dry heaves or Gagging” (Rhodes and McDaniel, 2001).

4.4. Chemotherapy Induced Nausea and Vomiting

Chemotherapy induced nausea and vomiting (CINV) is a disruptive and offensive side effect in patients receiving chemotherapy. CINV is associated with decreased adherence to effective chemotherapy regimens (Herrstedt, 2002). The economic impact of CINV includes remarkable increase in both direct and indirect cost of patient’s care. Acquisition cost of antiemetic drugs and administration devices are examples of direct cost while nursing and medico time, and in some

cases, elongated hospitalization or readmission are the indirect costs (Heffinger et al.,2004; Tina Shih et al.,2007).

4.5. Categories of Chemotherapy Induced Nausea and Vomiting

The CINV can be classified into three major categories, acute, delayed and anticipatory nausea and vomiting. Breakthrough and refractory nausea and vomiting are the two other categories that can be arise in uncontrolled symptoms. Time of occurrance and treatment of various type of CINV summarized in Figure 4.1.

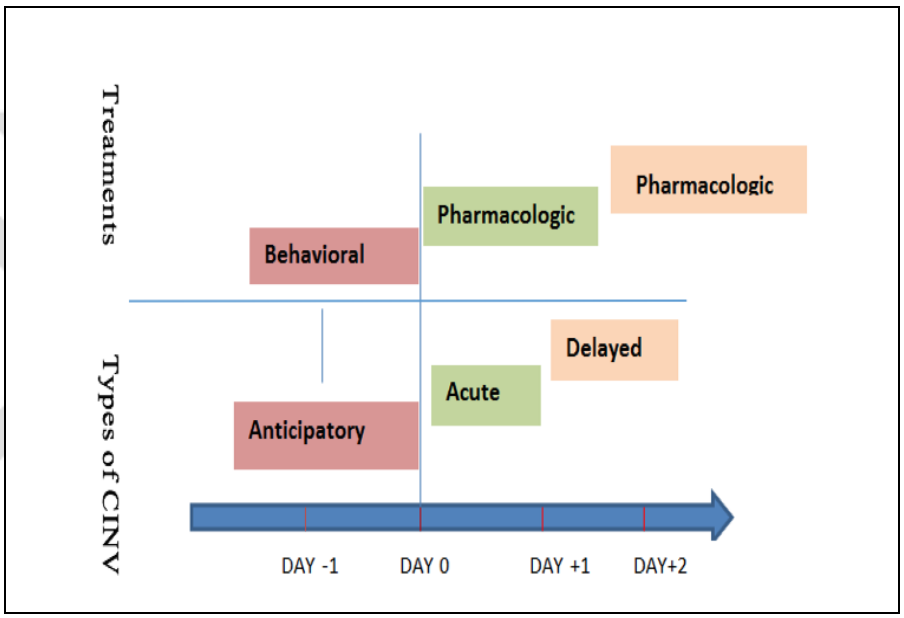

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Figure 4.1. Major types of CINV; Time of occurance and treatments

4.5.1. Acute Nausea and Vomiting

Its define as the nausea and vomiting that occur within the first 24 hour(hr) postchemotherapy administration and it can further subdivide into two subclasses. Acute which occur within the first 12 hr, and late acute occur from 12-24 hr (Yalçin et al.,1999; Hesketh, 2000). The main risk factors that contributes to acute emesis are the type, dose and emetogenicity of the administered chemotherapy but other risk factors include poor control prior to chemotherapy, female gender and adolescent age (Kris et al., 2006).

Cisplatin is the first agent identified for its acute emesis, risk which induce nausea and vomiting within 1 to 2 hours after receiving chemotherapy. The emesis

typically subsides after 18 to 24 hours and recur to reach second peak at approximately 48 to 72 hours after receiving the agent (Hesketh, 2008).

4.5.2. Delayed Nausea and Vomiting

A delayed CINV defined as nausea or vomiting that start after the first 24 hours of chemotherapy, and may persist for 6-7 days, some reports suggested that delayed CINV can be occur as soon as 16 hr postchemotherapy (Gregory and Ettinger. 1998). A delayed nausea and vomiting is associated with cisplatin, cyclophosphamide, and other drugs (e.g. doxorubicin and ifosfamide) given at high doses or given on 2 or more consecutive days. Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis (Wickham, 1999). Delayed CINV can occur in the absence of acute CINV (Kris et al., 1985). The pathophysiology of acute and delayed symptoms might differ, resulted in difference in the effect of standard antiemetics (Italian Group, 2000).

4.5.3. Anticipatory Nausea and Vomiting

Anticipatory Nausea and Vomiting is a learned or conditioned response to visual, gustatory, olfactory and environmental factors, associated with previously administered chemotherapy (Hesketh, 2000). It is appears to be the result of antecedent experiences with chemotherapy that led to nausea and vomiting, and commences as a patient is prepared for the next cycle of chemotherapy (Morrow and Rosenthal, 1996; Morrow et al., 1998). It can occur before, during or after the administration of a subsequent cycle of chemotherapy (Yalçin et al., 1999).

Risk factor for anticipatory nausea and vomiting include younger patients who have experienced severe and frequent nausea/vomiting after their anterior treatments, apprehensiveness, self absorption and replication expectancies (Andrykowski, 1990; Montgomery et al., 1998; Watson, 1993).

4.5.4. Refractory and Breakthrough CINV

Breakthrough is a term refers to vomiting that occurs despite the utilization of drugs to avert nausea and vomiting and may require administration of another

antiemetic drug or drugs to control the condition (rescue medication) (Navari, 2014). Refractory CINV is a minor condition that occurs in treatment cycles after the unsuccessful utilization of antiemetic or rescue medications in the precedent treatment cycle (Sigsgaard et al.,2000).

4.6. Pathophysiology of Nausea and Vomiting

Nausea and vomiting resulting from chemotherapy involves an intricate and multifaceted physiology. Considerable progress has been made in elucidating the mechanisms by which chemotherapy initiates the emetic reflex. This construal includes both the anatomy and neurotransmitters involved in CINV.

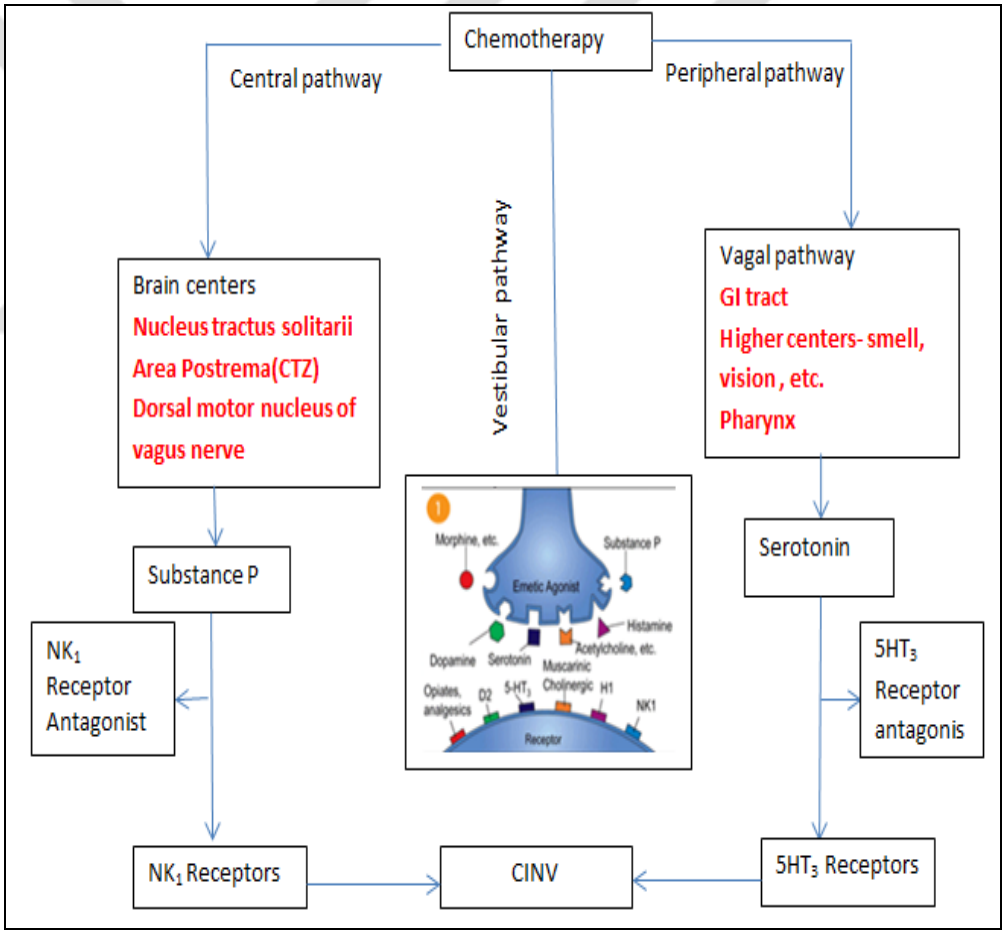

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Figure 4.2. Pathophysiology of nausea and vomiting

4.6.1. Neuroanatomy of CINV

Chemotherapy stimulate generation of free radicals resulted in release of 5 hydroxytryptamine (5-HT) from the enterochromaffin cells in gastric and bowel lumen, which subsequently stimulate 5-HT_3 receptors on vagal afferent and initiate vomiting reflex (Higgins et al.,1989).

Vomiting Reflex is initiated by a stimulation of chemoreceptor trigger zone (CTZ) in area postrema. These CTZ contains receptors for dopamine, serotonin, opioids, acetylcholine and substance P. A stimulation of those receptors leads to nausea and vomiting (Horn et al., 2007).

4.6.2. Neurotransmitters

There are more than 30 neurotransmitters involved in the mechanism of CINV but dopamine, serotonin and substance P are three neurotransmitters with the most clinical pertinence as the antagonist for these transmitters have shown clinical benefits as antiemetic (Leslie, 1985).

Serotonin (5-hydroxytriptaine)

The serotonin (5HT) is engendered by enterochromaffin cells, upon exposure to a chemotherapeutic agent these cells express 5HT abundantly. The secreted 5HT bind to $5HT_3$ receptors located on vagus nerve terminal and act as a neurotransmitter transducing signal to hindbrain (Gershon, 2004). The serotonin receptors were studied deeply between 1980-1990, and these studies led to the development of the type 5-hydroxytryptamine-3 ($5HT_3$) receptor antagonists during the early 1990s (Andrews et al., 1988). Nowadays these drugs become the mainstay of the antiemetic therapy for CINV. Tryptophan hydroxylase inhibitors (THI) which selectively inhibit 5HT in the gut is incipient target for many preclinical studies (Liu et al., 2008).

Dopamine

Until recently, dopamine was the neurotransmitter that appeared to be mostly responsible for CINV. Several dopamine antagonists were developed and they have a high degree of variability in the affinity of dopamine receptor binding (Ison and

Peroutka, 1986). Therefore chemotherapy agent that induced nausea and vomiting are affected very little or not at all by dopamine antagonists.

Substance P

Substance P is a member of A group of peptides known as tachykinins, its bind to kinin 1 receptor. Kinin 1 receptor is widely distributed throughout the central nervous system and additionally in peripheral site such as gastrointestinal tract (Quartara and Maggi, 1998).Peripheral and central component may be involved in the mechanism of substance P and neurokinin emetic potential. Selective antagonists of the NK1 receptor are potent antiemetics in preclinical models utilizing a variety of emetic stimuli (Watson et al., 1995).

The first drug devised to antagonise the NK-1 receptor is aprepitant, and it has proven effectively in obviating CINV when combined with currently used therapies (Poli-Bigelli et al., 2003).

4.7. Predictive Factors for CINV

There is a number of factors have been identified which increase the likelihood of developing CINV in certain situations. These factors can be related to the intirinsic emetogenicity and route of administration of the chemotherapy agent or to the patient population.

4.7.1. Factors Related to The Emetogenicity of Chemotherapy Agent

The chemotherapy agents were placed into four categories according to their level of emetogencity, high (>90%), moderate (30-90%), low (10-30%) and minimal (<10%).

For any given drug, the route and rate of administration, as well as the dose can influence emetogenicity (Jordan et al., 1985).

For combination chemotherapy, the level of emetogenicity is estimated according to the highest emetogenic-level drug in the combination. The contribution of other drugs in the risk of emesis is also evaluated in combination therapy. For

example, although cyclophosphamide and doxorubicin are two moderately emetogenic drugs, the protocol including both of the drugs is considered highly emetogenic (Basch et al., 2011; Roila et al., 2010).

4.7.2. Patient Related Factors

Emesis occurred prior to chemotherapy increases the risk of CINV and is one of the strongest predictors of nausea and vomiting (Morrow et al., 1998). It has been shown that females have a higher tendency to vomit than males. Therefore, being female, young and non-alcohol drinker are the most identifiable risk factors to CINV in chemotherapy naive patients (Kirkova et al., 2012). Patients with rapid metabolizers of certain 5-HT_3 receptor antagonists are more susceptible to severe CINV (Kaiser et al., 2004), and certain polymorphisms in the 5-HT_3 receptor can also confer a greater risk of CINV (Tremblay et al., 2003). A control of acute vomiting is associated with a reduction in vomiting within a five-days of post treatment. The occurrence of both acute and delayed vomiting may increase the possibility of anticipatory vomiting in the next chemotherapy cycle (Morrow et al., 1998; Fallowfield, 1992). It has been suggested that a history of motion sickness may predispose to anticipatory emesis (Morrow, 1984).

4.8. Severity Classification of CINV

A grading scheme for classifying the severity of CINV according to the National Cancer Institute Common Terminology Criteria for Adverse Events **(NCI CTCAE)** are presented in Table 4.1.

Table 4.1. Grading schema for classifying the severeity of CINV

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feedings, TPN, or hospitalization indicated		
Vomiting	One to two episodes (separated by five minutes) in 24 hours	Three to five episodes (separated by five minutes) in 24 hours	≥6 episodes (separated by five minutes) in 24 hours; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Adapted from (NCI CTCAE, 2010)

4.9. The Physiological and Psychological Impact of CINV

CINV impose an encumbrance on patients, clinicians, and the health care system. The negative impact of CINV affects the patient's ability to consummate activities of daily living, obtaining adequate rest, participation in convivial activities and perform work. The physiologic effects of CINV, including malnutrition. esophageal tears and metabolic derangements (e.g. chloride, potassium, volume depletion and metabolic alkalosis) can exacerbate the nephrotoxicity of chemotherapeutic agents (Wiser, 2005). In some cases, patients may refuse to continue potentially beneficial treatment regimens because of treatment associated nausea and vomiting (Hamadani et al., 2007). The physiological and psychological impact of CINV are summarized in Figure 4.3.

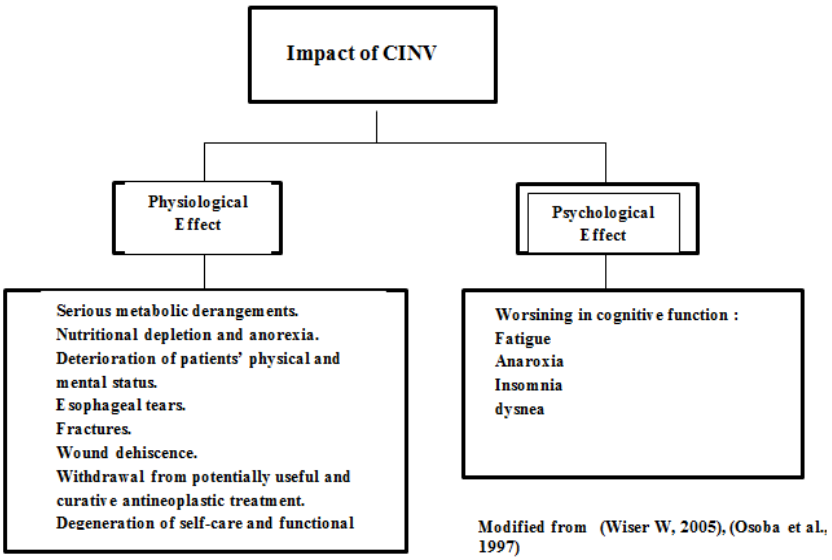

Figure 4.3. The physiological and psychological impact of CINV

4.10. Economic Impact of CINV

Poorly controlled or uncontrolled CINV require rescue medication and possible emergency health care practitioners'visits, which lead to increase in cost of medical care. The occurrence of CINV result in great absenteeism and may impede a patient's ability to work. (Tina Shih and Elting, 2007).

A study evaluated the overall burden of chemotherapy induced nausea and vomiting and cost of associated causes from a hospital's perspective was done in the United State hospital outpatient setting. Patients (n=11.495) diagnosed with cancer, aged ≥18 years initiating chemotherapy (CT) in a hospital outpatient setting for the first time between April the 1st /2007 and March the 31st /2009. Data were extracted from the Premier Perspective Database. Patients were followed through eight CT cycles or 6 months' post-index date, whichever occurred first. Within each CT cycle, the follow up time for CINV event estimation was from day 1 (except rescue medication use that was identified from day 2) to cycle end. During the follow up period, a total of 47.988 CINV events with an associated total all treatment cost of $89 million were observed. An average daily treatment cost for all care settings was $1854.7 (Craver et al., 2011).

The economic issues that should be considered when selecting antiemetic regimen discussed in Table 4.2.

Table 4.2. Economic issues for selection of Antiemetic Regimen

Will the regimen reduce the length of hospitalization?
Will patients be able to maintain their usual level of activity during treatment?
How will nursing and pharmacy costs be affected?
Are there any formulary restrictions or restriction for use in clinical settings?
How will the regimen affect out of pocket expenses for the patient?

Modified from (Vincent T, DeVita Jr, Theodore S,Lawrence, Steven A, Rosenberg, Ronald A, DePinho, 2001)

4.11. Impact of CINV on Patients' Quality of Life

Several studies have investigated the impact of nausea and vomiting on the patients' quality of life (QoL), albeit several methodologies were utilized in these studies, but all these studies approved its negative impact on the patients' quality of life. Functional Living Index-Emesis (FLIE) is commonly used but other quality of life assessment questionnaire such as European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQC30) has also been used (Osoba et al., 1997; Bloechl-Daum et al., 2006; Ballatori et al., 2007; Cohen et al., 2007; Fernández-Ortega et al., 2012).

Rusthoven et al, conducted a study to compare the mean scores between the unmodified EORTC QLQC-30 and the nausea and vomiting domains. The results showed that the HR-QOL rating attributed to nausea and vomiting accounted for much (though not all) of the deterioration in HR-QOL scores in patients who experienced these symptoms. Nevertheless, some of the decrease in health related QoL might be related to other factors which were unrecognized (Rusthoven et al., 1998).

Ballatori et al, conducted a study where FLIE questionnaire was used to evaluate the quality of life in adult cancer patients at seven Italian oncology centers, patients received cisplatin containing regimens, the result of this study shows that despite advances in antiemetic therapy, CINV remains an important problem in Italy. More

than two thirds of the patients' daily activities were affected negatively. Acute and delayed vomiting had a similar impact on daily life, but more patients with delayed nausea reported a more negative impact on daily life than those with acute nausea (Ballatori et al., 2007).

Fernández-Ortega et al., performed open multicenter prospective observational study. The results show that nausea had an impact on QoL on 72% of the cycles in which are nausea was developed; 47.4% of the cycles where nonsignificant nausea was present and 89.1% of cycles where nausea was significant. The longer the period of time with significant nausea, the higher the impact on QoL. Emesis had an impact on QoL on 60.6% of the cycles in which emesis was present. When the impact on QoL measured by the emesis domain of the FLIE score, it was found that occurance of emesis is decreased significantly in patients' QoL (Fernández-Ortega et al., 2012).

4.12. Nonpharmacological Treatment of CINV with "Complementary Therapies"

According to the National Center for Complementary and Alternative Medicine., complementary and alternative medicine (CAM) includes those diverse medical and health care systems, practices and products not generally regarded as conventional medicine (Engel and Straus, 2002).

In a study conducted in USA, showed that four out of ten adult and one out of nine child had used CAM during the study period of 12 months (Barnes et al., 2008). There is a high prevalence for using CAM or alternative treatment within the Turkish population (Algier et al., 2005; Gücük et al., 2013).

Traditional and common popular treatments such as herbs, acupuncture, chiropractic and massage are included in this category of therapy.

4.12.1 Herbal

Herbs were used traditionally for many purposes; food, culinary spices, medicinal, cosmetics, spiritual and ornamental. In developing countries 80% of the

population used traditional medicine and medicinal plants for their health management (Montazeri et al., 2013).

4.12.1.1 Ginger (*Zingiber officinale*)

Ginger is one of the herbs which shows an effect in treatment of chemotherapy induced nausea and vomiting. The pharmacological activity of ginger is related to its active components, gingered and shogalos. Their effects include anti-inflammatory, antiemetic, antipyretic, antitussive, antihypertensive, anticancer, decrease prostaglandin and relieve gastric discomfort by decreasing stomach contraction and increasing gastrointestinal tract activity (Montazeri et al., 2013).

There are at least five randomized trials were undertaken to investigate the effect of ginger in reducing nausea in patients receiving chemotherapy. Three of these trials showed positive results but two showed negative results.

In their study including 744 patients who had suffered nausea following chemotherapy, Ryan et al., gave 0.5, 1 or 1.5 gram doses twice daily of either a placebo or supplemental ginger for 6 days. On the day 1 of all cycles, each patient was given a 5-HT_3 receptor antagonist. It was determined that during chemotherapy, ginger supplementation was of significant help in reducing acute day 1 nausea, especially at doses of 0.5 and 1 gram (Ryan et al., 2012).

In another study, ginger root was also shown to be of benefit in combination with ondansetron and dexamethasone. In the placebo-controlled randomized trial, 57 children and young adults who were prescribed cisplatin/doxorubicin chemotherapy for bone sarcoma were given 334 or 800 mg (depending on the patient's weight) of ginger 1 hour prior to chemotherapy, and 3 and 8 h after the chemotherapy was commenced. When compared with conventional antiemetics, the ginger was found to significantly lower the rate of both acute and delayed emesis (Pillai et al., 2011).

In a different trial, ginger (1.5 g daily for 4 d post chemotherapy) was added to the conventional antiemetic therapy and given to 78 advanced breast cancer patients. The authors determined as a result, nausea was reduced for up to 24 h post chemotherapy (Panahi et al., 2012).

On the other hand, conflicting results with those of the above mentioned studies were reported by Zick et al., who concluded that the effectiveness of ginger in conjunction with standard antiemetics (5-HT_3 antagonists and/or aprepitant) could not be established. Cancer patients (*n* = 162) who had suffered CINV during at least one previous chemotherapy cycle were the subjects in this randomized placebo-controlled phase II trial; as a result those given ginger in addition to aprepitant suffered more severeely from acute nausea than those who were given aprepitant alone (Zick et al., 2009).

Furthermore, ginger was not shown to be beneficial in another trial in which conventional antiemetics in addition to ginger capsules (1 g daily) or placebo were randomly given for 3 d to 36 adult cancer patients who were under a cisplatin-based chemotherapy regimen. After 3 weeks, the regimen was switched to the alternative group for the next treatment cycle. The findings indicated that neither acute nor delayed nausea or emesis was reduced by the ginger (Fahimi et al., 2011).

4.12.1.2 Concord Grape Juice Flavonoid

Double blind randomized clinical trial was conducted to determine the feasibility of administration of concord grape juice for the management of CINV. Cancer patients (n=77) who received moderately or highly emetogenic chemotherapy agent were enrolled and the patients assigned into two groups, one group drank 4 Oz of grape juice and the other group recevied placebo. The frequency of nausea and vomiting and duration of distress were lower for experimental group, but there were no significant statistical differences in frequency over time ($p > 0.05$) due to a high attrition rate of 50% (Ingersoll et al., 2010).

4.12.2 Acupuncture and Related Therapies

Acupuncture depends on inserting fine needles into the body at particular points and left there for a short period of time. Acupuncture seems to have good effects in physical problems such as pain or reduction of symptoms such as anxiety, nausea.

Acupuncture was used firstly as traditional East Asian medicine and had been used in Chinese medicine before 2000 years ago (Ma, 2009).

Many studies have been conducted to evaluate acupuncture's ability to control nausea and emesis induced by chemotherapy. Different types of acupuncture techniques such as electroacupuncture, acupressure and electrostimulation were used in those studies (Ma, 2009). P_6 and $ST_{36,}$ acupuncture points were abundantly used in for nausea and vomiting.

It is unfortunate that the results of randomized trials are subject of bias and due to lack of standardization of treatment method and comparison group. In a systematic review which include studies that have been done in 2013, 8 out of the 11 trials were considered to have a high risk of bias (Garcia et al., 2013).

One of the strongest studies that support the use of acupuncture for chemotherapy induced nausea and vomiting is (Shen et al., 2014) where electroacupuncture, minimal needling and mock electrical stimulation were compared with antiemetic medications alone in patients undergoing a high emetogenic chemotherapy regimen. All patients received concurrent triple combination of antiemetic pharmacotherapy and high-dose chemotherapy (cyclophosphamide, cisplatin, and carmustine). The result showed that adjunct electroacupuncture was more effective in controlling emesis than minimal needling or antiemetic pharmacotherapy alone, but the effect had a limited duration, no significant effect was seen during the 9 day follow up period (Shen et al., 2014).

4.12.3 Behavioral Interventions

Behavioral interventions that use to reduce the side effects of cancer include contingency management, cognitive/attential distraction, hypnosis/distracting imagery, relaxation training, cognitive restructuring and modeling.

4.12.3.1 Cognitive/attential distraction

Cognitive distraction is a behavioral interventional method used to control nausea. It engages the patients in highly interesting activities during invasive procedures, so the patient's attention to abhorrent stimuli is blocked by their involvement in the task, those activities include guided imagery which primarly used in adults, storytelling usually used in children, video game playing and playing with

a party blower. The effect of distraction lasts as long as the patients attention is focused on the distraction task (Redd et al., 1994).

A prospective cohort study was conducted to determine the effect of coping strategies on the CINV, forty children aged 7-12 years were assigned to receive either moderate or highly emetogenic chemotherapy protocol with coping strategies, the most frequently used coping strategies were distraction and wishful thinking but the most effective strategies were social support and distraction. The difference were not statistically significant over time (Rodgers et al., 2012).

4.12.3.2 Systemic Desensitization

Systemic Desensitization (SD), involves introducing a feard stimuli gradually from least feard and progressing to the most feard resulting in altering patients' abhorrent reaction to stimuli. To evaluate the effect of SD on CINV, sixty ambulatory cancer patients with anticipatory nausea and vomiting before their third and fourth chemotherapy treatments were randomized equally into the three groups. One group received systemic desensitization, the second group received counseling and the third group received no treatment. Significantly more patients receiving desensitization reported no anticipatory nausea before their fifth and sixth chemotherapy treatments than the patients given counseling ($p<0.05$) or the patient with no treatment ($p<0.01$). The author concludes that systematic desensitization appears to have an antiemetic effect in cancer patients who receive chemotherapy, and may be useful in the management of these problems (Morrow and Morrell, 1982).

4.12.3.3 Yoga

Yoga is a system of exercises for mental and physical health, it IS a Hindu philosophy that teaches a person to experience inner peace by controlling the body and mind. Out of three articles reviewed on the effect of yoga, two showed that yoga had a significant effect on CINV (Usharani et al., 2012; Raghavendra, 2013) while the other showed that yoga had a significant effect in reducing nausea but no effect on vomiting (Raghavendra et al., 2007).

4.12.3.4 Progressive Muscle Relaxation Training

Progressive muscle relaxation (PMR) is a technique of alternately tensing and relaxing muscles groups in sequence throughout the body. When going through muscle groups, individuals can commence with the head and neck and progress to the feet, or vice versa. Some randomized control trials that used progressive muscle relaxation training prophylactically to control chemotherapy induced nausea and vomiting (Lyles et al.,1982; Holli, 1993; Molassiotis et al.,2002), did not approve the efficacy of PMR in decreasing the intensity of nausea and vomiting and all these studies were limited by its small sample size.

4.12.3.5 Music and Visual Therapy

The studies that examine the efficacy of music interventions in controlling CINV are very few. Albeit the preliminary finding indicates that music therapy can be adjacent to pharmacological antiemetic treatment, the circumscription of these studies due to the small sample and impotent designs makes its impotent evidence. (Standley, 1992; Ezzone et al.,1998; Gimeno, 2010; Karagozoglu et al., 2013).

4.13. Pharmacological Treatment of CINV

Pharmacological therapy for chemotherapy induced nausea and vomiting is directed towards occurance of acute, delayed, anticipatory and breakthrough nausea and vomiting.

4.13.1 Pharmacological Treatment of Acute Emesis

The three major pharmacological groups that extensively evaluated by clinical trial for the management of acute emesis include $5HT_3$ receptor antagonist, NK1 receptor antagonists and glucocorticoids. Most of those trials focus on either highly or moderately emetogenic chemotherapy agent.

4.13.1.1 5 -HT_3 receptor antagonists

Since it was discovered in mid 80s that seratonin (5-hydroxy tryptamine $5HT_3$) was partially responsible for induction CINV, it is realized that serotonin receptor antagonists could inhibit CINV (Gregory and Ettinger, 1998).

The management of CINV has rapidly advanced since the introduction of $5HT_3$ receptor antagonists. A long with dexamethasone, $5HT_3$RA represent the most effective regimen for the prevention of acute vomiting induced by cisplatin and moderately emetogenic chemotherapy (Roila et al.,1997).

The first generation $5HT_3$ receptor antagonists (dolasetron, granisetron, ondansetron, ramosetron and tropisetron) and second generation agent (palonosetron) are available globally. Dolasetron, granisetron, ondasetron, tropisetron and palonosetron are the only forms available in Turkey and granisetron, ondansetron and palonosetron are the most frequently utilized. Different types of $5HT_3$ receptor antagonists are summarized in Table 4.3 and Table 4.4.

Table 4.3. Types and Dosage Forms of $5HT_3$ receptor antagonists

Drug Name	**Dosage Form**
Tropisetron	5 mg ampule i.v. 5 mg capsule Oral
Dolasetron	3 mg/3 ml i.v. infusion 4 mg, 8 mg Oral disintegrating tablet 4 mg. 8 mg tablet 4 mg. 2 ml ampule
Ondansetron	4 mg, 8 mg tablet 4 mg/2 ml ampule 4 mg, 8 mg Oral disintegrating tablet 4 mg, 8 mg Wafers
Granisetron	1 mg, 2 mg tablet 3 mg/3ml ampule i.v. infusion
Palonsetron	250 mcg/5 ml vial

Modifed from www.uptodate.com

Table 4.4. Dose and Schedule of $5HT_3$ Receptor Antagonists

Drug	Dose and schedule	
	Prechemotherapy	**Postchemotherapy**
Ondansetron i.v.$^{\Delta}$	8 mg or 0.15 mg/kg i.v. once	8 mg by mouth twice daily on days 2 and 3 for moderately emetogenic chemotherapy with the potential for delayed emesis
Ondansetron oral$^{\Delta}$	8 mg by mouth twice daily	8 mg dissolved in mouth every 12 hours as needed
Ondansetron oral dissolving tablet (ODT)		8 mg dissolved in mouth every 12 hours as needed
Ondansetron oral soluble film		
Granisetron i.v.		1 mg by mouth twice daily on days 2 and 3 for moderately emetogenic chemotherapy with the potential for delayed emesis
Granisetron oral	2 mg by mouth once	100 mg by mouth daily on days 2 and 3 for moderately emetogenic chemotherapy with potential for delayed emesis
Granisetron transdermal patch	Apply 24 to 48 hours prior to chemotherapy. Releases 3.1 mg per 24 hours.	Remove 24 hours or more after last chemotherapy dose. Maximum seven days depending on regimen
Dolasetron oral ONLY $^{\Delta}$	100 mg by mouth once	
Palonosetron i.v.$^{\Delta}$	0.25 mg i.v. once	
Palonosetron oral	0.5 mg by mouth once	0.5 mg by mouth daily on days 2 and 3 for moderately emetogenic chemotherapy with potential for delayed emesis
Tropisetron i.v.**	5 mg i.v. once	
Tropisetron oral**		5 mg by mouth daily for up to 5 days
Ramosetron**	300 mcg i.v. once	

*i.v. use of dolasetron is contraindicated because of the potential for fatal cardiac arrhythmias.

** Not available in US, $^{\Delta}$Available in Turkey Modifed from www.uptodate.com

The first generation $5HT_3$ receptor antagonist have some differences and similarities as they have different structures and receptor binding affinity. Granisetron, dolasetron and its major metabolite are pure $5HT_3$ receptor antagonists, while ondansetron and tropisetron are weak antagonists at the $5HT_4$ receptor, ondasetron binds at other serotonin receptors and to the opoid μ receptor (Roila et al., 1997; Freeman et al., 1992). The half lives of granisetron, tropisetron and the active metabolite of dolasetron are 2.3 times longer than that of ondasetron (Gregory and Ettinger, 1998). The variability in structure and pharmacokinetics properties did

not affect the effectiveness in CINV. At recommended doses all the first generation $5HT_3$ antagonists appear to have equal efficacy at preventing CINV.

A meta-analysis of randomized controlled trials show that granisetron is equivalent to ondansetron for prophylaxis of CINV (Del Giglio et al., 2000). At a definable dose level all first generation $5HT_3$ antagonists have a plateau in their therapeutic efficacy, further dose escalation does not improve outcome (Gandara et al., 1998).

A multiple dose schedule is therapeutically equivalent to a single dose of first prevention $5HT_3$ antagonists when given prior to chemotherapy (Ettinger et al., 1996; Seynaevel et al., 1992; Thomas et al., 1992). Clinical trials also show that oral formulation of these drugs are as effective as intravenous formulation (Gandara et al., 1998; Gralla et al., 1998).

The efficacy of $5HT_3$ receptor antagonists is significantly improved when they are combined with glucocorticoids (Ioannidis et al.,2000). The common adverse effect of the first generation $5HT_3$ includes ECG changes, QT interval changes and cardiac arrhythmias with the exception of transdermal patches of granisetron (GTDS) which is not associated with statistically or clinically significant effects on QT or other electrocardiographic variables (Mason et al., 2012; Mason and Moon, 2013). Agents such as ondansetron and dolasetron that block sodium channels may produce QRS widening, and by blocking potassium channels lead to QT prolongation, Ondansetron and dolasetron may prolong QT intervals by up to about 5% (Boike et al.,1997).

The injectable form of dolasetron is contraindicated in children and adult as it is associated with QT interval prolongation (http://www.fda.gov/safety/ medwatch/safetyinformation/ucm187424.htm., Access date: 18/3/2016). The oral form of dolasetron is less likely to associate with abnormal heart rate, but still not completely safe and its use restricted by the Food and Drug Administration (FDA). Dolasetron must not be used unless potassium and magnesium level is normal, availability of electrocardiographic monitoring in case of patient with heart failure or a slow heart rate, underlying cardiac disease, elderly and renal impairment and it

must be avoided in patients with congenital QT syndrome or in patient who use drug to prolong PR interval such as verapamil or QRS interval such as flecainide and quinidine (http://www.fda.gov/safety/medwatch/safetyinformation/ ucm187424.htm., Access date: 18/3/2016).

In 2006, the Turkish Ministry of Health makes an announcement for the utilization of i.v. dolasetron exhibit the risk of QT interval prolongation and restricted its use in many conditions (https://www.titck.gov.tr/PortalAdmin/Uploads/Titck/Dynamic/%C4%B0la%C3%A7%20G%C3%BCvenli%C4%9Fi%20%C4%B0zleme.%20De%C4%9Ferlendirme%20%C5%9Eube%20M%C3%BCd%C3%BCrl%C3%BC%C4%9F%C3%BC%20%20T%C3%9CFAM/1370_3c72cf8.pdf., Access date: 18/3/2016). The utilization of i.v. dolasetron is dramatically decremented since the announcement and the prelude more safest $5HT_3$ antagonist.

Intravenous ondasetron is also associated with QTc prolongation and potentially fatal cardiac arrhythmias. QT interval prolongation is dose dependent and expected to be a rate dependent manner as well. It occur specifically with a single i.v. dose of 32 mg and high infusion rate (http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm330772.htm., Access date: 18/3/2016).

In the United States, single i.v, doses are limited to not more than 16 mg. The use of ondansetron is precluded in patients with congenital long-QT syndrome, and ECG monitoring should be applied in patients with hypokalemia or hypomagnesaemia, heart failure, bradyarrhythmias, and in those taking other drugs known to increase the risk of QTc prolongation.

The utilization of ondasetron for acute emesis in Turkey displayed a dramatic decrease after the FDA Safety Announcement (http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm330772.htm., Access date: 18/3/2016). According to the instruction of the Turkish Ministry of Health, the dose of i.v. ondansetron must not exceed a single dose of 8 mg for geriatric patients (above 75 years) given within at least 15 minutes' infusion. The dose can be increased to 16 mg (i.v. infusion within 15 minutes) for adults and patients younger

than 75 years (https://www.titck.gov.tr/PortalAdmin/Uploads /Titck/Dynamic/2c71418e87283.pdf., Access date: 18/3/2016).

Tropisetron shows similar efficacy with other $5HT_3$ receptor antagonists for the prevention of CINV in both adults and children. It is suitable as first-line therapy (combined with a corticosteroid) for the prevention of acute nausea and vomiting in patients treated with moderate to severe emetogenic chemotherapeutic agents. This combination is also moderately effective in the prevention of delayed nausea and vomiting (Simpson et al., 2000).

The studies that compare tropisetron, dolasetron and ondansetron efficacy in Turkey is constrained. Yalçın et al compared the efficacy of tropisetron (5 mg), ondansetron (8 mg), and granisetron (3 mg) in 54 breast cancer patients receiving single-day chemotherapy. All but one patient in the granisetron group were female. A Complete control of acute vomiting was achieved in 38.8% of patients with ondansetron, 58.8% with tropisetron, and 73.7% with granisetron. Major response rates were 83.3%, 82.3%, and 89.5%, respectively. For the delayed control of emesis. complete control of delayed vomiting was achieved in 38.8% with ondansetron. 52.9% with tropisetron, and 73.7% with granisetron. The major response rates were 71.8%, 70.5%, and 100%, respectively. The adverse effects were rare and mild in all groups. The result of this study displays that there is clinical differences among $5HT_3$ antagonists antiemetic effects (Yalçın et al, 1999).

Oge et al., conducted a study which compared tropisetron (5 mg), ondansetron (8 mg), and granisetron (3 mg) in 106 patients receiving cisplatin. Complete response rate (CR) were 61.1%, 51.4%, and 65.7% in the first 24 hours for tropisetron, ondanseton and granisetron, respectively. The result from study showed that there is no significant statistical difference in effectiveness of these three antiemetics (Oge et al., 2000).

In July 2013, FDA approved palonosetron hydrochloride injection for the treatment of CINV (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-372_Alox.cfm., Access date: 18/3/2016)). Palonosetron differ from the first generation drugs by its higher receptor binding affinity (30-100 fold), longer half life

(40 hr) and its unique pharmacokinetic properties in healthy subject and in cancer patients (Leon, 2003). QTc prolongation has not been described with palonosetron and it did not cause any severe rhythmic disorders or symptomatic ECG changes (Gonullu et al., 2012).

When compared with dolasetron, a single dose of palonosetron is as effective as a single dose of dolasetron in preventing acute CINV and superior to dolasetron in preventing delayed CINV after moderately emetogenic chemotherapy, with a comparable safety profile for all treatment groups (Eisenberg et al., 2003).

In comparison with ondansetron i.v. 32 mg dose, a single dose of palonosetron 0.25 mg was significantly superior in prevention of acute and delayed CINV (Gralla, 2003).

A systematic review of eight qualified trials reporting outcomes on 3592 patients showed statistically significant differences in favor of palonosetron compared with first generation $5HT_3$ receptor antagonists in prevention of acute CINV and delayed CINV. There is no difference between 0.25 mg and 0.75 mg dose of palonosetron on the prevention effect, but there is significant differences in the incidence of constipation (Likun et al., 2011).

Aapro et al., conducted Phase III randomized control trial in which different doses of palonosetron (0.25 mg, 0.75 mg) and ondansetron 32 mg were given in a total of, 673 patients into three treatment arms. Firstly, no significant differences in antiemetic control were noted between palonosetron arms and ondansetron arms in the acute phase, while complete response was slightly higher with palonsetron than ondansetron for delayed phase (24-120 hr) and overall phase (0-120 hr). In the two third of the patients who recieved concomitant dexamethasone, significantly more higher complete response rate were seen in palonsetron -dexamethasone arm than ondansetron – dexamethasone in the delayed and overall phase (Aapro et al., 2006).

Saito et al., trial is another Phase III randomized control trial which studied the effect of addition of corticosteroid to palonsetron in prevention of chemotherapy induce nausea and vomiting. A total of 1143 patients who received high emetogenic chemotherapy (cisplatin or cyclophosphamide plus anthracycline) were participated.

A complete response is occurred similarly in palonosetron-corticosteroid arm and granisetron-corticosteroid arm in the acute phase, but during the delayed phase, more complete responses were significantly achieved in palonsetron arm (Saito et al., 2009).

Oral palonosetron has a comparable efficacy and safety profile as i.v palonosetron 0.25 mg and can be a preferred formulation in certain clinical situations. Palonsetron 0.5 mg oral has been preferred for the prevention of CINV in patients receiving moderately emetogenic chemotherapy because of the remote increase in efficacy without an increase in side effects (Boccia et al., 2013).

In general, $5HT_3$-RA, whose side effects are minimal and include low-grade headache, malaise and constipation, is considered to be safe. In all trials, $5HT_3$-RA was given with concomitant medications (http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm418818.htm., Access date: 18/3/2016); therefore the potential risk for serotonin syndrome associated with $5HT_3$-RA has not been clearly shown. The symptoms of serotonin syndrome include confusion, agitation, restlessness, twitching or stiffness of the muscles, fever, sweating, heart rate and blood pressure fluctuations. nausea and/or vomiting, loss of consciousness, and coma anf if not treated can results in death. Thus, caution must be taken when prescribing $5HT_3$-RA in conjunction with other drugs that may possibly affect serotonin levels.

With the first-generation $5HT_3$-RA, a greater number of ECG interval changes and cardiac arrhythmias were observed than with the second-generation drug. The most pronounced ECG interval changes are manifested within 1 to 2 h of taking the drug, but these are mostly small and clinically insignificant, the values had returned to baseline within 24 hour (Navari and Koeller, 2003; Pinarli et al., 2006). Moreover, there have been reports of potentially fatal cardiac arrhythmias, including torsade de pointes, linked to QTc prolongation (Turner et al., 2007; Keller et al., 2010). The risk is increased when these drugs are take concomitantly with other drugs that increase in QTC prolongation.

4.13.1.2 Neurokinin -1 Receptor Antagonists (NK -1RA)

The first NK1 RA that has been introduced for the prevention of chemotherapy induced nausea and vomiting were oral "aprepitant" and parental "fosaprepitant" (Hesketh et al.,2003), they prevent not only the acute emesis but also the delayed emesis in patients treated with highly emetogenic chemotherapy drugs, and work best when its given with dexamethasone and $5HT_3$ RA (Poli-Bigelli et al., 2003).

Fosaprepitant was approved from the FDA for the prevention of CINV associated with highly and moderately emetogenic chemotherapy. It is an intravenous prodrug of the orally administered antiemetic aprepitant (Colon-Gonzalez and Kraft, 2010). An intravenous dose of fosaprepitant 115 mg was shown to have bioequivalence to oral aprepitant 125 mg (Lasseter et al., 2007).

There is no significant difference in the safety profile between aprepitant and non aprepitant based antiemetic regimen, the adverse events are mild and infrequent and the tolerability of fosaprepitant and aprepitant were shown to be the same (as fosaprepitant is rapidly converted to aprepitant following administration) (Chrisp, 2007). Fosaprepitant has an equivalent safety profile to the comparator drug ondansetron when used to treat CINV in highly emetogenic chemotherapy, except for an increased incidence of diarrhea (60% with fosaprepitant versus 9% with ondansetron) (Cocquyt et al., 2001). A systemic review of seventeen trials (8740 patients) showed that the use of NK1 RA did not increase the risk of diarrhea in cancer patients, but the rates of hiccups and fatigue were significantly increase, the rate of severe infection also increases but not associated with an increased rate of neutropenia or febrile neutropenia (Dos Santos et al., 2012).

Aprepitant is available in 80 mg, and 125 mg capsules, the recommended dosing regimen is 125 mg one hour before chemotherapy on treatment day one and 80 mg once daily on day two and three.

In a trial conducted by Campos et al., patients receiving cisplatin chemotherapy were randomly given (on one of two schedules) aprepitant combined with granisetron, granisetron alone, or aprepitant alone. Before the cisplatin was administered, 20 mg of dexamethasone was given orally to all patients. Vomiting

was prevented in 80% of the patients with the three-drug combination. whereas the combination of dexamethasone with either granisetron or aprepitant was not so effectual, preventing emesis in only 57% and 43 to 46% of the cases, respectively (Campos et al., 2001).

As the NK1 receptor antagonist is a moderate inhibitor for CYP3A4, caution should be considered when prescribing for patients who are taking drugs that are metabolized by the same enzyme.

Because CYP3A4 enzyme triggers the metabolism of glucocorticoids, when given concomitantly with aprepitant in clinical trials, the dexamethasone dosage on d 1 was reduced from 20 mg to 12 mg and on d 2 and 3, from 8 mg twice daily to 8 mg daily (Hesketh et al., 2003; Warr et al., 2005). The dose was reduced only when the glucocorticoids were given together with NK1 receptor antagonists acting as an antiemetic. However, the dosage was not reduced when the glucocorticoids were given as an antitumor compound of the chemotherapy schedule.

Although no clinical proof has been observed, aprepitant could hypothetically reduce the clearance of drugs such as cyclophosphamide, docetaxel, etoposide, irinotecan and vinca alkaloids which are metabolized by CYP3A4, thus it can tesult in prolonging exposure and worsening toxicity (Warr et al., 2005; Nygren et al., 2005).

Another NK1 RA is “casopitant”, which to date has not been approved by the FDA and therefore is not commercially available. At present casopitant can be administered on day 1 as a single oral dose or as an oral dose together with dexamethasone and ondansetron in a three-day mixed intravenous schedule (Grunberg et al., 2009).

A study was conducted to determine the advantages of combining a NK1 RA antagonist such as aprepitant, fosaprepitant or casopitant with the $5HT_3$ receptor antagonist and a glucocorticoid in order to prevent acute CINV. In a meta-analysis of 17 clinical trials, the outcomes of patients (n = 8740) receiving highly or moderately emetogenic therapy were evaluated. The results showed that the addition of NK1 RA into antiemetic therapy increased the degree of complete response in both the

delayed and overall stages of emesis. With regard to secondary outcomes such as frequency of vomiting and absence of nausea, the addition of NK1 RA performed better than the control, showing benefits in cases of highly emetogenic as well as moderately emetogenic chemotherapy. No difference between aprepitant/fosaprepitant and casopitant was observed in terms of effectiveness of the treatment (Dos Santos et al., 2012).

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors. The fixed oral dose combination called as NEPA is comprised of 300 mg of netupitant, and 0.5 mg of palonosetron. For control of both acute and delayed nausea and emesis post chemotherapy (highly or moderately emetogenic), a single dose of NEPA on d 1 combined with dexamethasone is as effective and safe as three days of aprepitant in conjunction with a $5HT_3$ receptor antagonist and dexamethasone (Gralla et al., 2014; Hesketh et al., 2014).

In October 2014, NEPA was authorized in the United States as a preventative treatment for chemotherapy-related nausea and emesis. When administered in combination with a glucocorticoid, NEPA can be used as an alternative to aprepitant and fosaprepitant in patients receiving highly emetogenic chemotherapy agents like cisplatin or anthracycline combined with cyclophosphamide.(http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418375.htm., Access date: 18/3/2016).

Rolapitant is a new neurokinin receptor antagonist. In a study reported at the European Society of Medical Oncology Congress 2014, rolapitant was significantly better than placebo, a complete response was achieved more in the rolapitant group than of the placebo for patients in the delayed phase of CINV (72.7% vs 58.4%; P < .001), the acute phase (83.7% vs 73.7%; P = .005), and in the overall phase (70.1% vs 56.5%; p = 0.001). The drug approved recently by FDA in 2015 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460838.htm, Access date: 18/3/2016).

4.13.1.3. Glucocorticoids

Glucocorticoids are extensively used alone for drugs of low emetogenic potential and in combination with $5HT_3$ receptor inhibitors and/or NK1 receptor antagonists in moderate or highly emetic chemotherapy cycles. All glucocorticoids produce a similar effect if given in appropriate doses; however, as dexamethasone has been the most extensively tested, it is the glucocorticoid that is most preferred glucocorticoid.

The findings of one study revealed that for a complete protection from both acute emesis (risk ratio [RR] 1.30) and delayed emesis (RR 1.30), dexamethasone performed better than a placebo or no treatment (Ioannidis, 2000). The meta-analysis of 32 randomized trials, in which patients (n = 5613) who received moderately or highly emetogenic chemotherapy, concluded that dexamethasone alone was still not sufficient in controlling CINV in most of these patients (Basch et al., 2011). On the other hand, dexamethasone has been found to significantly enhance the antiemetic effectiveness of the $5HT_3$ receptor antagonists.

4.13.1.4. Second Line Therapy for Acute Emesis

In the treatment or prevention of CINV, phenothiazines (e.g., prochlorperazine), metoclopramide, butyrophenones and cannabinoids are used as second-line therapy. As they have a lower therapeutic index than $5HT_3$ receptor antagonists and glucocorticoids, these drugs should be administered only in patients intolerant of or refractory to those first-line agents. Due to the lack of research showing the safety and efficacy of synthetic oral cannabinoids, their use in this setting is still controversial (Herman et al., 1979; Pomeroy et al., 1986; Todaro, 2012). When a glucocorticoid is contraindicated, phenothiazines can be used as a single agent in place of dexamethasone for a regimen with low risk of emesis (Basch et al., 2011).

Although it is not recommended to be used as single-agent, lorazepam and diphenhydramine may be beneficial when they are used in conjunction with conventional antiemetic drugs (Basch et al., 2011).

4.13.2 Pharmacological Treatment of Delayed Emesis

Emesis that occurs more than 24 hours post chemotherapy is classified as delayed emesis. A delayed emesis is more common after high-dose cisplatin therapy (Koo and Ang, 1996; Olver et al., 1996), however it can also results from other agents (Kaizer et al., 1994).

Without effective prophylaxis, there is a 60-90% risk of developing delayed emesis following cisplatin at doses of >70 mg/m^2. However, the risk falls to 20-30% in patients undergoing chemotherapy with anthracycline plus cyclophosphamide (Italian Group, 2000).

A delayed emesis is also linked to moderate emetogenic agents including doxorubicin (≥40 mg/m^2 as a single agent or ≥25 mg/m^2 in conjunction with other chemotherapeutic agents, especially cyclophosphamide), epirubicin (≥75 mg/m^2 as a single agent or ≥50 mg/m^2 when combined with other agents), combinations of cyclophosphamide (≥600 mg/m^2 combined with other drugs), carboplatin (≥300 mg/m^2), oxaliplatin (oxaliplatin together with short-term infusional fluorouracil and leucovorin, as used in the FOLFOX regimen for advanced colorectal cancer), and cisplatin (at doses between 20 and 50 mg/m^2) (Kaizer et al., 1994; Pater et al., 1997).

A number of studies have examined the need for additional methods of controlling delayed emesis and nausea. In one study, 28 of 68 patients (41%) who experienced no post-chemotherapy vomiting in the 24 hour after administration of ondansetron and dexamethasone as premedication, vomited in the next four days when no further antiemetics were administered. When ondansetron was continued, this number was reduced to 15 of 75 (20%) (Kaizer et al., 1994).

High Risk Delayed Emesis

The American Society of Clinical Oncology (ASCO) has issued guidelines for patients receiving cisplatin recommending the use of an NK1 receptor antagonist (either aprepitant on d 1 to 3 or fosaprepitant on d 1 only) plus, a glucocorticoid on d 1 to 4, and a $5HT_3$ receptor antagonist on d 1 (Basch et al., 2011).

A delayed emesis in patients receiving cisplatin often cannot be prevented by glucocorticoids alone (Olver et al., 1996). Regardless of ondansetron administration in the control group after day 1, their rates in the overall phase is (i.e., 120 h post chemotherapy) increased with the addition of NK1 RA; however, the addition of the NK1 RA is appeared to be more beneficial in patients not given ondansetron after d 1 (Dos Santos et al., 2012).

In order to compare the efficacy of aprepitant with that of dexamethasone, a randomized double-blind study evaluated 551 of 580 participating chemotherapy naive breast cancer cases being treated with anthracycline plus cyclophosphamide. All patients were given aprepitant, a $5HT_3$ receptor antagonist, and dexamethasone therapy on day 1, on day 2 and day 3, patients were randomly given oral dexamethasone 4 mg twice daily or aprepitant 80 mg once daily. The primary end point of the study was a complete response (i.e., no vomiting or rescue treatment) from d 2 to 5 post chemotherapy. These results revealed that in the delayed period, dexamethasone is just as effective as aprepitant, and especially under conditions where resources are limited, its use for breast cancer patients is proposed. It remains to be seen if a combination of delayed phase aprepitant plus dexamethasone, or fosaprepitant on day 1 followed by delayed-phase dexamethasone is superior to aprepitant on day 1 and then dexamethasone alone for the delayed phase (Roila et al., 2015).

The effects of aprepitant and metaclopromide were compared in another randomized control trial in which the management of delayed emesis after cisplatin was evaluated. When used in combination with dexamethasone on day 1 post chemotherapy, significant difference in complete response rates (80.3 vs, 82.5 for aprepitant and metaclopromide, respectively) were reported (Roila et al., 2015). Nonetheless, additional randomized control trials must be conducted before these data are clinically applied.

In cases where highly emetogenic chemotherapy such as cisplatin or combined anthracycline plus cyclophosphamide are being administered, NEPA (300 mg of netupitant+ 0.5 mg of palonosetron) can be considered as an alternative to aprepitant- and fosaprepitant-containing regimens (Gralla et al., 2014; Hesketh et al., 2014). The

FDA approved NEPA for the prevention of chemotherapy-related nausea and emesis (http://www.fda.gov/News Events/Newsroom/PressAnnouncements/ucm418375. htm., Access date: 18/3/2016), but although its use is not recommended after d 1 when used in conjunction with anthracycline plus cyclophosphamide chemotherapy. However, dexamethasone is recommended on d 1 through 4 when used with a regimen which includes cisplatin.

The use of 5HT3 receptor antagonists alone as monotherapy has shown some benefit, although not as great as that observed with glucocorticoids (Navari et al., 1995; Olver et al., 1996; Goedhals et al.,1998; Geling and Eichler, 2005). For prevention of delayed emesis in patients undergoing cisplatin therapy, the use of $5HT_3$ receptor antagonists alone is not recommended.

For the prevention of delayed emesis due to cisplatin-based chemotherapy, the second-generation $5HT_3$ receptor antagonist palonosetron appears to be better than other $5HT_3$ receptor antagonists. Palonosetron 0.25 mg has been shown to be superior to ondansetron for controlling delayed and overall vomiting in patients given concomitant dexamethasone treatment (Aapro et al., 2006; Saito et al., 2009).

The results of a phase III trial carried out on patients (n = 247) given cisplatin or doxorubicin plus cyclophosphamide, indicated that antipsychotic olanzapine was superior to aprepitant for the prevention of delayed nausea. The patients treated with olanzapine exhibited a significantly higher rate (69% vs. 38%) of nausea control in the delayed period (Navari et al., 2011). Another randomized control trial found olanzapine to be superior to dexamethasone, with similar complete response rates (91% and 89%, respectively) for acute emesis. A complete delayed response was more likely with olanzapine (79% vs. 57%), but this difference was not statistically significant. Furthermore, olanzapine resulted in significantly better (70% vs. 30%) delayed nausea control compared to dexamethasone (Lijun et al., 2009). However, additional broad-range studies are needed before these data can be clinically applied.

Moderate Risk Delayed Emesis

A single-agent treatment with dexamethasone on d 2 and 3 has been recommended for this population. When using a first-generation $5HT_3$ receptor

antagonist on day 1 instead of palonosetron, a reasonable alternative would be to treat with a first-generation $5HT_3$ receptor antagonist alone on d 2 and 3 (Italian Group, 2000; Roscoe et al., 2012).

Low Risk Delayed Emesis

It has been recommended that patients receiving low emetogenic risk drugs should be treated only with dexamethasone (8 mg). In some patients the use of glucocorticoids is contraindicated or undesirable (e.g., those undergoing long-term weekly chemotherapy). In such cases, a single dose of a drug such as prochlorperazine can be given as an alternative (http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf., Access date: 22/3/2016). In general, this patient population is not in need of prophylaxis against delayed emesis.

Minimal Risk Delayed Emesis

Antiemetic therapy for the prevention of acute or delayed CINV is not recommended for routine administration to most patients receiving chemotherapy agents with low emetogenicity. However, prophylactic antiemetics such as dexamethasone (8 mg), prochlorperazine, or metoclopramide may be given to patients on an "as-needed" basis or to those who have previously experienced emesis with low-risk regimens (Basch et al., 2011).

Anticipatory Emesis

By ensuring good control of acute and delayed emesis starting from the initial chemotherapy cycle, anticipatory nausea or vomiting can be effectively prevented. However, non- pharmacological methods including hypnosis and behavioral therapy with systemic desensitization can be effective when anticipatory emesis has already been established (Morrow and Morrell, 1982; Burish and Jenkins, 1992).

An administration of benzodiazepine may be beneficial prior to and during chemotherapy (Razavi et al., 1993; Malik et al., 1995). One double-blind trial evaluated anticipatory emesis in 57 primary breast cancer patients undergoing adjuvant chemotherapy. When low-dose alprazolam (0.5-2 mg/d) was administered

along in a psychological support program that includeds progressive relaxation training, the results showed a significantly reduced rate of anticipatory nausea compared with placebo (0 vs. 18%, respectively) (Razavi et al., 1993).

Table 4.5 Recommended Antiemetic Treatment for Single–Day. Intravenously Administered Chemotherapy

Risk category	Agent	Dosing on day of chemotherapy	Dosing on subsequent day
High Emetic Risk > 90 %	NK1 receptor antagonist		
	Aprepitant Fosaprepitant	125 mg oral 150 mg i.v.	80 mg oral daily. day 2 and 3
	Plus		
	$5HT_3$ antagonist (one of the following)		
	Granisetron	2 mg oral;1mgor 0.01mg/kg i.v.	
	Ondansetron	8 mg oral twice daily; 8 mg or 0.15 mg/kg i.v.	
	Palonosetron	0.5 mg oral; 0.25 mg i.v.	
	Dolasetron	100 mg oral only	
	Tropisetron	Tropisetron 5 mg oral; 5 mg i.v.	
	Ramosetron	0.3 mg i.v.	
	Plus		
	Dexamethasone	12 mg oral or i.v.	8 mg oral or i.v. on day_1 (all patients); day_2 2-3 or day 2-4 (cisplatin only)
	Or		
	NEPA (netupitant plus palonosetron)	Once	
	Plus		
	Dexamethasone	12 mg oral or i.v.	8 mg oral or i.v. on day_1 (all patients); day_2 2-3 or day 2-4 (cisplatin only)
Moderate Emetic Risk 31-90 %	$5HT_3$ antagonist		
	Palonosetron	0.5 mg oral; 0.25 mg i.v.	
	Plus		
	Dexamethasone	8 mgoral or i.v.	8 mg oral or i.v. on day 2-3
Low Emetic Risk 10-30%	Glucocorticoids		
	Dexamethasone	8 mg oral or i.v.	
Minimal Emetic Risk <10%	None	None	None

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4.13.3 Special Situations

Consecutive Day Therapy with Highly Emetogenic Agents

With moderately or highly emetogenic chemotherapy drugs like cisplatin and dacarbazine, the administration of prophylaxis on several consecutive days becomes very difficult. This problem may be attributed to anticipatory emesis on the days following therapy or to the intensified acute and delayed effects of the treatment. Updated American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend that, when applicable, antiemetics appropriate for emetogenicity assigned chemotherapy can be given on each day of the chemotherapy and on the following 2 d (Basch et al., 2011).

Before NK1 receptor antagonists became available, a number of trials had suggested that the best approach was to administer repeated daily doses of a $5HT_3$ receptor antagonist in conjunction with dexamethasone (Hainsworth, 1992; Räth et al., 1993).

In order to evaluate the benefit of aprepitant in conjunction with a $5HT_3$ antagonist and dexamethasone, a small trial was carried out using germ-cell cancer patients (n = 69) on a five-day cisplatin regimen (Albany et al., 2012). All patients were given a $5HT_3$ antagonist other than palonosetron from day 1 through 5. Additionally, dexamethasone 20 mg was administered (once a day on day 1 and 2), and aprepitant (125 mg on d 3, 80 mg on d 4 and 5) or no aprepitant were randomly assigned to patients. The group given aprepitant was also given dexamethasone (4 mg twice daily on d 6, 7, and 8), while the placebo group was given dexamethasone (8 mg twice daily on d 6 and 7, and 4 mg twice daily on d 8). The results of the trial noted that a significantly higher number of the patients receiving aprepitant (42% vs 13%) elicited a complete response (no emetic episodes and no rescue medication used). Moreover, the numerical score for degree of nausea on the visual analog scale (VAS) was lower for aprepitant, although the difference was not statistically significant compared to the placebo. This study presented a rationale for starting the NK1 RA on d 3 rather than on d 1; however, no optimal schedule has been established for the use of NK1 RA in patients receiving highly emetogenic

chemotherapy on consecutive days. Thus, there is a need for further comparative trials in this arena.

In five-day cisplatin regimens, like those applied for testicular germ-cell cancer, it is recommended to administer a daily oral dose of a $5HT_3$ receptor antagonist or a granisetron transdermal patch in conjunction with dexamethasone, with additional aprepitant or fosaprepitant starting on d 1 (Albany et al., 2012).

5. MATERIALS AND METHOD

Aim of the study is to determine the pharmaceutical needs for patients receiving antiemetic to treat chemotherapy induced nausea and vomiting.

The study was conducted at the Marmara University Pendik Research and Training Hospital between 15 May - 30 September 2015.

Aprior to conducting the study, the ethical committee approval was obtained from the Faculty of Medicine, Marmara University, Istanbul, Turkey in 5/9/2014 (Appendix 1). An official letter of request was obtained from Pharmaceuticals and Medical Devices Agency, Turkish Ministry of Health in 14 /5/2015 (Appendix 2).

Participants were informed about the purpose of the study and assured that their personal details were remained confidential. Participation was completely optional. Consent forms and confidentiality were maintained at all times during the study (Appendix 3).

5.1. Study Design

This observational prospective Study was conducted at the Marmara University Pendik Research and Training Chemotherapy Unit which receives both oncology and hematology patients. On day 1 of the first chemotherapy cycle, patients were assessed carefully to be included in the study. Patient's demographic details were collected using patient profile record (Appendix 4). Laboratory results were evaluated and creatinine clearance was calculated using Crockcroft –Gault formula

$$\text{CRCL} = \frac{(140 - \text{age}) \times \text{Mass (in kilograms)} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine (in mg/dl)}}$$

Patients who have White Blood Cell (WBC) $\leq 3 \times 10^9$ cells per L, Alanine aminotransferase (ALT) or Aspartate Aminotransferase (AST) >100 U/L, Creatinine Clearance CrCL<60 ml/min were excluded. Patient previous medical and medication history were collected. All the patients were informed about the research aims and protocol and their permission for participation were taken.

Medication history was taken and carefully evaluated for possible interactions with antiemetics drugs that prescribed for delayed nausea and vomiting. Drug interactions were assessed using Multi-Drug Interaction Checker - Medscape® Reference which discussed in Section 5.2.3. According to the database, I checked the severeity of interactions and recorded any intervention done by the medical team to prevent its occurrence. Patient's profiles were checked, chemotherapy profile was assessed and chemotherapy emetogenicity level was determined.

The prescribed antiemetics were reviewed and evaluated for its adherence to MASCC guidelines. Drug drug interaction between the chemotherapy protocol and the antiemetic drugs were evaluated.

Daily dairy was given to the patients at first day (Appendix 5). In this dairy, the patients were asked to record the number of vomiting episode, severity of nausea, type and number of rescue medication that were used in the first 24h and within 5 days postchemotherapy. The nausea was assessed using a Likert scale of seven points. In this Likert scale one is referred to the worst nausea and the seven referred to the best condition.

The patients were given FLIC questionnaire that contains 22 questions about cancer (Appendix 6) to be filled while waiting to have their chemotherapy. FLIE (Appendix 7) questionnaire was administered to the patients before chemotherapy before and 5 days postchemotherapy. Adverse effects record form (Appendix 8) was given to be filled at any time during chemotherapy cycles. The time span between the first and the second chemotherapy protocols depends on the type of chemotherapy but it ranges between 7–28 days.

On the second chemotherapy cycle, daily dairy, FLIE and adverse effects record form were collected from the patients and reviewed to assess the performance. Laboratory results of, "complete blood count, liver function tests, kidney function tests, electrolyte" were re-evaluated. Any changes from the baseline were recorded. The patient general condition, severeity of adverse effects were assessed and any changes from the base line were recorded. The same process was done in the third chemotherapy cycle.

After the data were completely collected, data recoding was started. The numbers were given for each outcomes to allow analysis, data recoding took few days then analysis started, SPSS program version 16 were used to analyse the data. the analysis included descriptive analysis, frequency, estimating percentage, correlation categorical analysis. Figure 5.1 describe the flow diagram of the study.

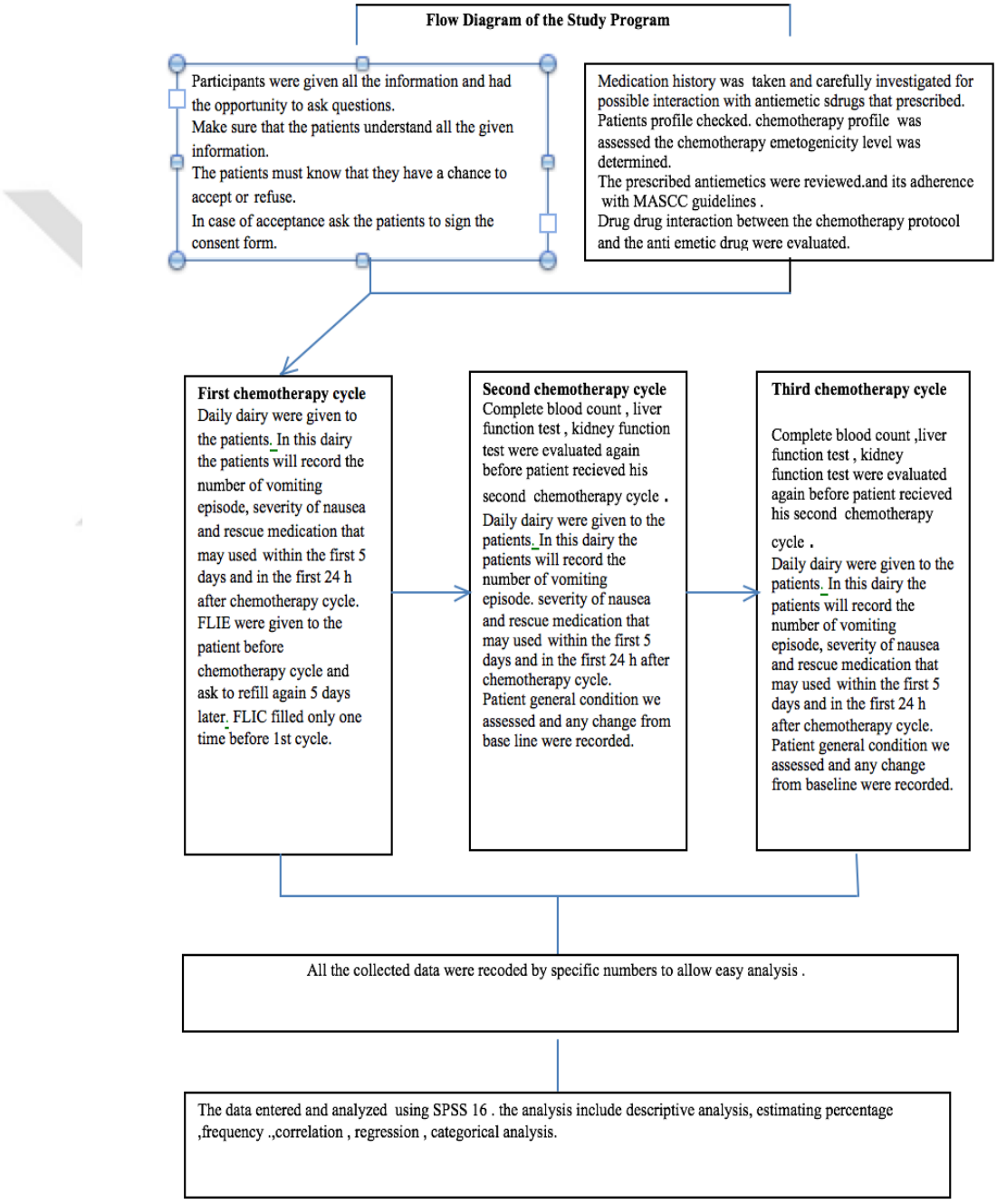

Figure 5.1: Flow Diagram of the Study

5.2. Study Population

The study participants have been selected according to the previous studies (Peterson et al., 1996; Gralla et al., 2003). Naive chemotherapy was preferred to exclude possible anticipatory nausea and vomiting. Patients with discrete diagnosis (oncology or hematology) and different level of emetogenic chemotherapy level were chosen.

Patients aged >18 and ≤ 75 years old were selected. The patients in this group of ages were able to record their symptoms and their quality of life scores by their selves.

According to the previous studies 100 patients seemed to be reasonable number for the sample size (Affronti et al., 2014, Almazrou and Alnaim, 2012, Bektas and Akdemir, 2008, Aksu et al., 2013).

5.2.1 Inclusion Criteria

Men and a women aged 18 to 75 years with confirmed malignant disease, patient's chemotherapy naïve or patients who had been treated with one low or minimally emetogenic antitumor drug were included. Patients who had adequate bone marrow function (white blood count ≥3x109 cells per L), adequate hepatic function (aspartate amino transferase (AST) and alanine aminotransferase (ALT) <100 U/L and adequate renal function (creatinine clearance ≥ 60 ml/min) were included.

5.2.2. Exclusion Criteria

Patient were excluded from the study if any of the following are presented; severe, uncontrolled concurrent illness other than neoplasia. Asymptomatic metastases to the brain, seizure disorder needed anticonvulsants unless clinically stable, gastric outlet or intestinal obstruction, any vomiting, retching or grade 2 or higher nausea, a known hypersensitivity to $5HT_3$ receptor antagonists or dexamethasone or aprepitant or any other antiemetic ingredient.

5.3. Assessment Parameters

` 5.3.1 Adherence to Guidelines Assessment

Multinational Association of Supportive Care in Cancer (MASCC) guidelines Index 9 2014 was used to assess adherence. Any differences from the guidelines in dose, route, duration and selection were considered as Nonadherence to guidelines. Nonadherence to guidelines was categorized as inappropriate dose, Inappropriate selection, Overprescription and Underprescription.

5.3.2 Antiemetic Effectivness Assessment

5.3.2.1 Antiemetic Effectivness Assessment Criteria

To assess the antiemetic drug effect, the following criteria were used; Complete control “no emetic episodes, no rescue therapy, no nausea”, Complete Protection “no emetic episodes, no rescue therapy and no significant nausea (Likert Score 2 or less)” Complete Response “no emetic episodes, nausea likert scale 2 or less , rescue therapy”, Partial response “nausea with Likert scale >2 and no emetic episode with rescue therapy”, Major response “ ≤2 emetic episode”, Minor response “ 3-5 emetic episode and Failure “ > 5 emetic episode. The complete control is the primary outcome of the study.

5.3.3 Quality of Life Assessment

5.3.3.1 Functional Living Index Questionnaire – Cancer

Functional Living Index is 22 items questionnaire that was designed to be self-administrated by the patients. This questionnaire contains different aspects; question on physical functioning (9 items), psychological functioning (6 items) , social (2 items) and hardship due to cancer (3 items). The original index has been validated on 837 patients over a three years (Donovan et al., 1989). The English version of FLIC was translated into the Turkish language and administered to 110 patients who had been receiving chemotherapy, the consistency and reliability was measured and it was in the acceptance range (Bektas and Akdemir, 2008). The Turkish version of FLIC was used after the permission was taken from the owners of validity.

5.3.3.2 Functional Living Index – Emesis

FLIE is a specific, valid questionnaire aimed at measuring the impact of CINV on patient's daily life. FLIE investigates two domains, 9 items for nausea and 9 items for vomiting domain. Each item is measured with a 100-mm Visual Analogue Scale which indicates the worst condition to the best condition, from 1 to 7 points. Therefore, each domain score ranges from 9 (maximum impact) to 63 (no impact). No (or minimal) impact on Patient's Daily Life (NIDL) is generally considered a score ≥54 (6 points for each item). In order to standardize the results, it is recommended that FLIE should be administered twice, before the chemotherapy administration and at day 6 from the chemotherapy administration (Preedy and Watson, 2010).

The Turkish version of FLIE was used in this study. The English version of FLIE was translated into Turkish language and administered to 60 patients who had been receiving chemotherapy, the consistency and reliability were measured and those were in the acceptance range (Aksu et al., 2013).

5.3.4. Determination of Adverse Effects

To determine the side effects of drugs, all the possible side effects that the drug can develop were included in a record form and the severity of the side effects were evaluated. The severity of side effects was categorized as mild, moderate and severe. The patients record any side effects that they suffer during the treatment period.

5.3.5. Assessment of Drug Interaction

Medscape is one of the most authoritative and accessible point of medical reference available to physicians and other health care professionals on the internet and mobile devices. Medscape Drug Interaction Checker® provide rapid access to tens of thousands of interactions between brand and generic drugs, over the counter drugs, herbal and supplements.

According to the Medscape drug interactions can be minor (the interaction is unlikely, minor or nonsignificant), significant (require monitoring by doctor), serious (require regular monitoring by doctor or alternate medication may be needed) and

contraindicated (never used combination of drugs because of high risk for dangerous interaction).

5.4. Statistical Analysis

Continuous variables were presented as mean±standard deviation whereas ordinal and nominal data were presented in n (%). Categorized data has been analyzed with the Chi Square test. For continuous variable data following normal distribution. Student t-test was used, while for data not following normal distribution, non-parametric test such as Mann-Whitney U and Kruskal Wallis tests were applied. The results have been evaluated at the 95% confidence interval with $p < 0.05$. For all statistical analyses. SPSS 16.0 statistical software was utilized.

Descriptive statistics were used to summarize the demographic variables, laboratory results.

Frequency tables and figures were constructed for demographic variables; education level, diagnosis, different comorbidities and adherence with guidelines for acute and delayed management of CINV.

Normality test were used to determine if a data set is well –modeled by a normal distribution and to compute how likely it is for a random variable underlying the data set to be normally distributed.

Chi- square statistics were used to assess any significant differences between the participants in different groups in relation to age, gender, smoking status, alcohol status, education level, duration and level of emetogencity, diagnosis and comorbidities.

Reliability test which was used to assess the consistency of results across items within a test and assessed the internal consistency reliability for both Functional Living Index Cancer (FLIC) and Functional Living Index Emesis (FLIE) where (cronbach's alpha of ≥ 0.6) is the acceptable value that indicates consistency reliability.

Mann–Whitney *U* test, nonparametric test was used to assess differences between groups without making the assumption that values are normally distributed

as differences between the adherence and nonadherence with guidelines in relation to quality of life and patient who recieved education and who not received in relation to antiemetic drug effect.

The Kruskal-Wallis H test, nonparametric test was used to determine if there are statistically significant differences in groups in different groups in terms of diagnosis, comorbidities in relation to CINV, effect of antiemetic drug and quality of life, severeity of side effects in relation to quality of life, drug interaction and quality of life.

Spearman test, was used to measure the strength of a relation between laboratory data and incidence of chemotherapy induced nausea and vomiting, and maintain correlations between number of drugs and incidence of drug drug interactions.

6. RESULTS

6.1 Demographic Variables

A total of 100 patients were observed; their demographic variables can be seen in Table 6.1.

Table 6.1. Patients Demographics and Clinical Characteristics.

Demographic/clinical characteristic	Patients (n=100)
Age in years. mean ± SD (median)	53.9±1.37 (53)
Gender n (%)	
Male	48 (%)
Female	52 (%)
Marital Status n (%)	
Married	92 (%)
Single, divorced, or separated	8 (%)
Smokers n (%)	24(24)
Chronic drinkers n (%)	8(8)
Comorbid conditions (%)	29%
One comorbidity	18%
Two comorbidities	6%
Multiple comorbidities ≥3	5%

6.1.1. Age and Antiemetic Therapy Effectivness

There is no significant differences in the antiemetic therapy effectivness and incidence of nausea neither in acute nor in delayed prevention of nausea between age groups. There is a significant difference in acute vomiting incidence between age groups only in first cycle of the chemotherapy as summarized in Table 6.2

Table 6.2. Impact of Age on Chemotherapy Induced Vomiting

Chemotherapy cycle	Acute vomiting	18-24 Years n	25-34 Years n	35-44 Years n	45-54 Years n	55-64 Years n	65-75 Years n	P value
1st cycle	no vomiting							
	1 vomiting	1%	6.2%	14.4%	23.7%	18.6%	36.1%	0.014*
	2 vomiting	0%	33.3%	66.7%	0%	0%	0%	
2nd cycle	no vomiting	1%	7.1%	16.2%	23.2%	18.2%	34.3%	0.281
	1 vomiting	0%	0%	0%	0%	0%	100%	
Third cycle cannot be computed								

6.1.2. Gender and CINV

There is no statistically significanct differences in nausea or vomiting between male and female patients neither in acute nor in delayed control of nausea and vomiting during two of the observed chemotherapy cycles in Table 6.3.

Table 6.3. Impact of Gender on Chemotherapy Induced Nausea and Vomiting

Chemotherapy cycle	**Acute nausea**	**Male (n)**	**Female (n)**	**P value**
1st	no nausea	48%	52%	0.693
	2 nausea	100%	0%	
	3 nausea	0%	100%	
2nd	no nausea	48.5%	51.5%	0.520
	6 nausea	0%	100%	
3rd	no nausea	48.5%	51.5%	
	3 nausea	0	100%	
Chemotherapy cycle	**Delayed nausea**	**Male (n)**	**Female (n)**	**P value**
1st	no nausea	51.2%	48.8%	0.342
	2 nausea	50%	50%	
	3 nausea	77.8%	22.2%	
	4 nausea	40%	60%	
	5 nausea	18.2%	81.8%	
	6 nausea	44.4%	55.6%	
	Severe nausea	50%	50%	
2nd	no nausea	50%	50%	0.464
	2 nausea	50%	50%	
	3 nausea	33.3%	66.7%	
	4 nausea	33.3%	66.7%	
	5 nausea	60.7%	39.3%	
	6 nausea	43.9%	56.2%	
	Severe nausea	12.5%	87.5%	
3rd	no nausea	47.6%	52.4%	0.696
	2 nausea	0%	100%	
	3 nausea	0%	100%	
	4 nausea	53.8%	46.2%	
	5 nausea	45%	55%	
	6 nausea	47.1%	52.9%	
	Severe nausea	66.7%	33.3%	
Chemotherapy cycle	**Acute vomiting**	**Male (n)**	**Female (n)**	**P value**
1st	no vomiting			0.530
	1 vomiting	48.5%	51.5%	
	2 vomiting	33.3%	66.7%	
2nd	no vomiting	48.5%	51.5%	0.520
	1 vomiting	0%	100%	
The third cycle cannot be computed.				

Table 6.3. Impact of Gender on Chemotherapy Induced Nausea and Vomiting ***(Continiued)***

Chemotherapy cycle	Delayed vomiting	Male (n)	Female (n)	P value
1st	no vomiting	49.3%	50.7%	0.540
	1 vomiting	54.5%	45.5%	
	3 vomiting	28.6%	71.4%	
	4 vomiting	0%	100%	
	5vomiting	100%	0%	
	6 vomiting	33.3%	66.7%	
	7 vomiting	50%	50%	
2nd	no vomiting	51.5%	48.5%	0.194
	1 vomiting	47.1%	52.9%	
	2 vomiting	44.4%	55.6%	
	3 vomiting	20%	80%	
	4 vomiting	33.3%	66.7%	
3rd	no vomiting	47.6%	52.4%	0.982
	1 vomiting	60%	40%	
	2 vomiting	20%	80%	
	3 vomiting	66.7%	33.3%	

6.1.3. Smoking and Alcohol

There is no statistically significant differences in the incidence of nausea and vomiting between smoker, non-smoker, alcohol drinker and non alcohol drinker as shown in Table 6.4.

Table 6.4. Impact of Smoking and Alcohol on Chemotherapy Induced Nausea and Vomiting

Chemotherapy cycle	**Acute nausea**	**Smoker (n)**	**Non smoker (n)**	**P value**
1st	no nausea	23.5%	76.5%	0.178
	2 nausea	0%	100%	
	3 nausea	100%	0%	
2nd	no nausea	24.2%	75.8%	0.760
	6 nausea	0%	100%	
3rd	no nausea	24.2%	75.8%	0.760
	3 nausea	0%	100%	
Chemotherapy cycle	**Acute vomiting**	**Smoker (n)**	**Non smoker (n)**	**P value**
1st	1 vomiting	23.7%	76.3	0.565
	2 vomiting	33.3	66.7	
2nd	no vomiting	24.2%	75.8%	0.760
	1 vomiting	0%	100%	
Chemotherapy cycle	**Delayed vomiting**	**Smoker (n)**	**Non smoker (n)**	**P value**
1st	no vomiting	24%	76%	0.720
	1 vomiting	27.3%	72.7%	
	3 vomiting	28.6%	71.4%	
	4 vomiting	0%	100%	
	5vomiting	0%	100%	
	6 vomiting	33.3%	66.7%	
	7 vomiting	0%	100%	
2nd	no vomiting	21.2%	78.8%	0.801
	1 vomiting	35.3%	64.7%	
	2 vomiting	22.2%	77.8%	
	3 vomiting	40%	60%	
	4 vomiting	0%	100%	
3rd	no vomiting	26.8%	73.2%	0.512
	1 vomiting	0%	100%	
	2 vomiting	20%	80%	
	3 vomiting	33.3%	66.7%	

Table 6.4. Impact of Smoking and Alcohol on Chemotherapy Induced Nausea and Vomiting ***(Continiued)***

Chemotherapy cycle	**Acute nausea**	**Alcohol (n)**	**No alcohol (n)**	**P value**
1st	no nausea	8.2%	91.8%	0.691
	2 nausea	0%	100%	
	3 nausea	0%	100%	
2nd	no nausea	8.1%	91.9%	0.920
	6 nausea	0%	100%	
3rd	no nausea	8.1%	91.9%	0.920
	3 nausea	0%	100%	
Chemotherapy cycle	**Delayed nausea**	**Alcohol (n)**	**No alcohol (n)**	**P value**
1st	no nausea	7%	93%	0.788
	2 nausea	12.5%	87.5%	
	3 nausea	11.1%	88.9%	
	4nausea	0%	100%	
	5 nausea	9.1%	90.9%	
	6 nausea	11.1%	88.9%	
	Severe nausea	10%	90%	
2nd	no nausea	5%	95%	0.579
	2 nausea	0%	100%	
	3 nausea	33.3%	66.7%	
	4nausea	0%	100%	
	5 nausea	10.7%	89.3%	
	6 nausea	12.5%	87.5%	
	Severe nausea	0%	100%	
3rd	no nausea	4.8%	95.2%	0.556
	2 nausea	100%	0%	
	3 nausea	0%	100%	
	4nausea	15.4%	84.6%	
	5 nausea	0%	100%	
	6 nausea	11.8%	88.2%	
	Severe nausea	16.7%	83.3%	
Chemotherapy cycle	**Acute vomiting**	**Alcohol (n)**	**No alcohol (n)**	**P value**
1st	1 vomiting	8.2%	91.8%	0.77
	2 vomiting	0%	100%	
2nd	no vomiting	8.1%	91.9%	0.920
	1 vomiting	0%	100%	

Table 6.4. Impact of Smoking and Alcohol on Chemotherapy Induced Nausea and Vomiting ***(Continiued)***

Chemotherapy cycle	**Delayed vomiting**	**Alcohol** (n)	**No alcohol (n)**	**P value**
1st	no vomiting	8%	92%	0.680
	1 vomiting	9.1%	90.9%	
	3 vomiting	14.3%	85.7%	
	4 vomiting	0%	100%	
	5vomiting	0%	100%	
	6 vomiting	0%	100%	
	7 vomiting	0%	100%	
2nd	no vomiting	9.1%	90.9%	0.488
	1 vomiting	5.9%	94.1%	
	2 vomiting	11.1%	88.9%	
	3 vomiting	0%	100%	
	4 vomiting	0%	100%	
3rd	no vomiting	8.5%	91.5%	0.866
	1 vomiting	0%	100%	
	2 vomiting	20%	80%	
	3 vomiting	0%	100%	

6.1.4. Educational Level

Sixty-five percent of the study population were poorly educated (9% illiterate, 56% elementary school), while only 4% was highly educated as seen in Figure 6.1.

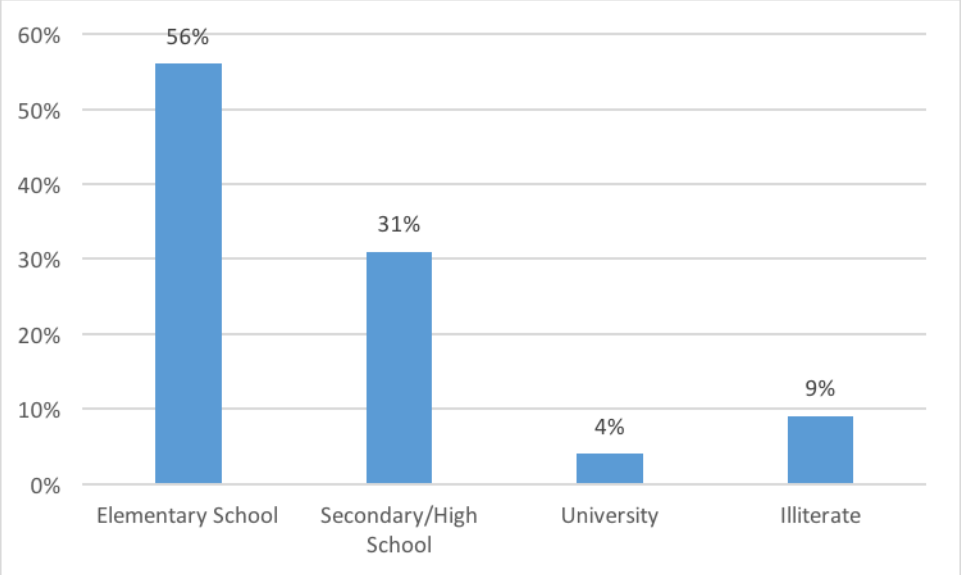

Figure 6.1. Education Level of the Study Population

6.1.5. Education Level and Antiemetic Therapy Effectivness

There are no significant differences in nausea and vomiting or antiemetic drug effect for both acute and delayed CINV between different educational level groups ($p>0.05$).

6.1.6. Education Level and Quality of Life

There are no significant differences in FLIE score between different educational level groups ($p>0.05$).

6.2. Diagnosis and Comorbidity

6.2.1. Diagnosis and CINV

The patients received different chemotherapy protocols due to having different diagnosis. The diagnosis was presented in Figure 6.2.

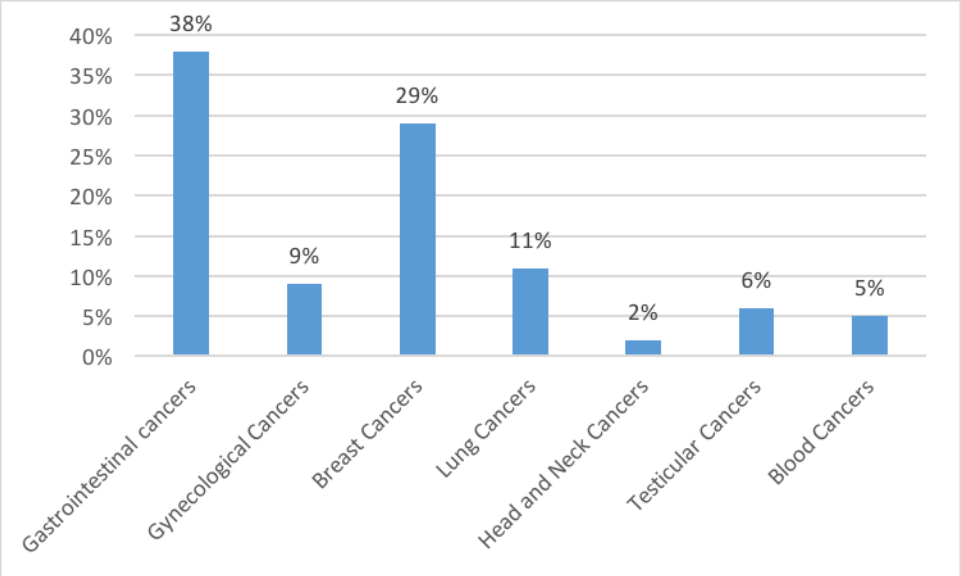

Figure 6.2. Patient's Diagnosis of cancer

Figure 6.2 showed that about 29% of the study population were female with breast cancer, 38% with gastrointestinal cancers (colon, stomach, small intestine, esophageal), while lung cancer accounted for 11% of the population, other diagnosis that involved in the study were gynecological cancer (uterine, ovary) (9%), testicular cancer (6%), head and neck (2%) and blood cancer (5%).

6.2.2. Diagnosis and Antiemetic Therapy Effectivness

There are no significant differences in nausea and vomiting or antiemetic drug effect for both acute and delayed CINV between different diagnosis that observed ($p>0.05$).

6.2.3. Diagnosis and Quality of Life

There are no significant differences in FLIE score between different diagnosis ($p>0.05$).

6.2.4. Comorbidities

Seventy-one percent of the study population did not have any comorbidities while multiple comorbidities were seen in 5% of the patients as seen in Table 6.5.

Table 6.5. Impact of Comorbidities on Chemotherapy Induced Nausea and Vomiting

Comorbidities	GAGA	GNGA	GAGD	GNGD	Total	P value
No Comorbidity	72.5%	65%	82.1%	66.7%	71%	0.51 (A)
One comorbidity	15%	22,6%	14.3%	19.4%	18%	0.24 (D)
Two comorbidities	6.2%	6.2%	3.6%	6.9%	6%	
Multiple comorbidities ≥3	6.2%	6.2%	0%	6.9%	5%	

GAGA: Guideline adherence group for acute control of CINV; GNGA: Guideline nonadherence group for Acute control of CINV; GAGD: Guideline adherence group for delayed control of CINV; GNGD: Guideline nonadherence group for delayed control of CINV. A: Acute; D: Delayed.

6.2.5. Comorbidities and Antiemetic Therapy Effectivness

There are no significant differences in incidence of nausea and vomiting or antiemetic drug effect for both acute and delayed CINV between different comorbidities ($p>0.05$).

6.2.6. Comorbidities and Quality of Life

There is no significant differences FLIE score between different comorbidities that observed ($p>0.05$).

6.3. Laboratory Results

Complete blood cell count (WBC, HGB, PLT), kidney function tests (urea, creatinine, uric acid), electrolyte and liver function tests (ALT, AST, GGT) were evaluated and the means value occurs within the normal range. The means for some of laboratory results were shown in Table 6.6.

Table 6.6. Laboratory Tests Means

Laboratory test (Referencerange)	Mean value	SD
WBC (4-10 $x10^3/\mu L$)	10.85	± 25.55
HGB (12-17g/dL)	12.34	± 1.7
Urea (6-23 mg/dL)	14.1	± 5.4
Creatinine (0-1.2 mg/dL)	0.72	± 1.49
Potassium (3.5-5.3 mEq/L)	4.22	±0.479
Creatinine Clearance (Men 97-137 mL/min) (Women 88-128 mL/min)	105 (90 -120)	±4.79

WBC: White blood cell; HGB: Hemoglobin

6.3.1. Impact of Laboratory Results on Antiemetic Therapy Effectivness

There are no differences seen between different laboratory tests results and antiemetic drug use neither for acute nor for delayed CINV in the three chemotherapy cycle that observed as seen in Table 6.7.

Table 6.7. Impact of Laboratory Tests on Antiemetic Therapy Effectivness

Chemotherapy cycle	Antiemetic effect	Blood test	P value
1st	Acute control	WBC*	0.74
		HGB*	0.18
		Urea	0.14
		Creatinine	0.41
		Potassium	0.15
		Creatinine Clearance	0.23
	Delayed control	WBC	0.82
		HGB	0.48
		Urea	0.39
		Creatinine	0.16
		Potassium	0.83
		Creatinine Clearance	0.5
2nd	Acute control	WBC	0.14
		HGB	0.09
		Urea	0.76
		Creatinine	0.89
		Potassium	0.43
		Creatinine Clearance	0.24
	Delayed control	WBC	0.99
		HGB	0.36
		Urea	0.6
		Creatinine	0.53
		Potassium	0.22
		Creatinine Clearance	0.77
3rd	Acute control	WBC	0.1
		HGB	0.2
		Urea	0.1
		Creatinine	0.47
		Potassium	0.31
		Creatinine Clearance	0.97
	Delayed control	WBC	0.82
		HGB	0.90
		Urea	0.42
		Creatinine	0.39
		Potassium	0.37
		Creatinine Clearance	0.13

WBC: White blood cell; HGB: Hemoglobin

6.4. Level of Emetogenicity

Table 6.8 describes the characteristics of patients according to their emetogenic protocols, where 50 patients received high emetogenic potential chemotherapy while 43 patient received moderate emetogenic and only seven patients received low emetogenic potential chemotherapy.

Table 6.8. Characteristics of Patients According to their Emetogenic Protocol

Protocol Emetogenic Potential	**High Emetogenic Potential**	**Moderate Emetogenic Potential**	**Low Emetogenic Potential**
Patients	50	43	7
Platinum based chemotherapy			
Cisplatin >50mg/m^2	32		
Cisplatin <50mg/m^2		4	
Oxaloplatin		24	
Carboplatin		10	
Cyclophosphamide + anthracycline	18		
Irinotecan			1
Paclitaxel			6
Others		5	
Sex			
Female	30	18	4
Male	20	25	3
Patients available for 3 cycle follow up			
I	50	43	7
II	50	43	7
III	49*	43	7

*One Patient lost at the third cycle

6.4.1. Level of Emetogenicity and CINV

The difference between different emetic potential risk groups as seen only during the second cycle as seen in Table 6.9.

Table 6.9. Impact of Emetogenic Potential on Antiemetic Therapy Effectiveness

Chemotherapy Cycle	Antiemetic effect for acute CINV	Low emetogenic risk	Moderate emetogenic risk	High emetogenic risk	P value
1st	CR	7.4%	43.6%	48.9%	0.509
	PR	0%	0%	100%	
	MR	0%	50%	50%	
2nd	CC	7.1%	43.4%	49.5%	0.358
	MR	0%	0%	100%	
3rd	CC	7.1%	42.4%	50.5%	0.488
	PR	0%	100%	0%	
Chemotherapy cycle	**Antiemetic effect for delayed CINV**	**Low emetogenic risk**	**Moderate emetogenic risk**	**High emetogenic risk**	**P value**
1st	CC	2.4%	57.1%	40.5%	0.249
	CR	0%	100%	0%	
	CP	40%	20%	40%	
	PR	3.7%	29.6%	66.7%	
	MR	18.2%	36.4%	45.5%	
	MIR	12.5%	37.5%	50%	
	TF	0%	33.3%	66.7%	
2nd	CC	10%	50%	40%	0.045*
	CR	0%	0%	100%	
	CP	50%	0%	50%	
	PR	4.8%	52.4%	42.9%	
	MR	3.3%	33.3%	63.3%	
	MIR	0%	33.3%	66.7%	
3rd	CC	9.5%	47.6%	42.9%	0.540
	CR	0%	0%	100%	
	CP	100%	0%	0%	
	PR	0%	51.4%	48.6%	
	MR	6.7%	13.3%	80%	
	MIR	0%	100%	0%	

CC: Complete Control "no emetic episodes, no rescue therapy, and no nausea", CR: Complete Response "no emetic episodes, nausea likert scale 2 or less, rescue therapy", CP: Complete Protection "no emetic episode, no rescue therapy and no significant nausea likert scale 2 or less", PR: Partial Response "nausea with likert scale >2 and no emetic episode", MR: Major Response "≤2 emetic episode", MIR: Minor Response "3-5 emetic episode", TR: Treatment Failure "> 5 emetic episode".

6.5. Duration of Chemotherapy Cycles and CINV

The length of chemotherapy cycle length differs according to diagnosis, there is no difference between the chemotherapy cycle length and CINV as shown in Table 6.10.

Table 6.10. Impact of Chemotherapy Cycle Length on Antiemetic Therapy Effectiveness

Antiemetic effect for ACINV (1st cycle) (n)	**Every 7 day chemotherapy cycle**	**Every 14 days chemotherapy cycle**	**Every 21 days chemotherapy cycle**	**Every 28 days chemotherapy cycle**	**P value**
CC	7.4%	5.3%	81.9%	5.3%	0.574
PR	0%	0%	100%	0%	
CR	0%	0%	100%	0%	
Antiemetic effect for ACINV (2nd cycle) (n)	**Every 7 day chemotherapy cycle**	**Every 14 days chemotherapy cycle**	**Every 21 days chemotherapy cycle**	**Every 28 days chemotherapy cycle**	**P value**
CC	7.1%	5.1%	82.8%	5.1%	0.816
MR	0%	0%	100%	0%	
Antiemetic effect for ACINV (3rd cycle) (n)	**Every 7 day chemotherapy cycle**	**Every 14 days chemotherapy cycle**	**Every 21 days chemotherapy cycle**	**Every 28 days chemotherapy cycle**	**P value**
CC	7.1%	4%	83.8%	5.1%	0.152
PR	0%	100%	0%	0%	
Antiemetic effect for delayed CINV (1st cycle) (n)	**Every 7 day chemotherapy cycle**	**Every 14 days chemotherapy cycle**	**Every 21 days chemotherapy cycle**	**Every 28 days chemotherapy cycle**	**P value**
CC	9.5%	4.8%	81%	4.8%	0.174
CR	100%	0%	0%	0%	
CP	0%	20%	80%	0%	
PR	7.4%	0%	81.5%	11.1%	
MR	0%	9.1%	90.9%	0%	
MIR	0%	0%	100%	0%	
TF	0%	16.7%	83.3%	0%	
Antiemetic effect for delayed CINV (2nd cycle) (n)	**Every 7 day chemotherapy cycle**	**Every 14 days chemotherapy cycle**	**Every 21 days chemotherapy cycle**	**Every 28 days chemotherapy cycle**	**P value**
CC	5%%	5%	85%	5%	0.404
CR	100%	0%	0%	0%	
CP	0%	0%	100%	0%	
PR	9.5%	4.8%	81%	4.8%	
MR	6.7%	6.7%	80%	6.7%	
MIR	0%	0%	100%	0%	

Table 6.10. Impact of Chemotherapy Cycle Length on Antiemetic Therapy Effectiveness (Continiued)

Antiemetic effect for delayed CINV (3rd cycle) (n)	Every 7 day chemotherapy cycle	Every 14 days chemotherapy cycle	Every 21 days chemotherapy cycle	Every 28 days chemotherapy cycle	P value
CC	4.8%	4.8%	83.3%	7.1%	0.592
CR	50%	0%	50%	0%	
CP	0%	0%	100%	0%	
PR	8.1%	8.1%	78.4%	5.4%	
MR	6.7%	0%	93.3%	0%	
MIR	0%	0%	100%	0%	

CC: Complete Control "no emetic episodes, no rescue therapy, and no nausea", CR: Complete Response "no emetic episodes, nausea likert scale 2 or less, rescue therapy", CP: Complete Protection "no emetic episode, no rescue therapy and no significant nausea likert scale 2 or less", PR: Partial Response "nausea with likert scale >2 and no emetic episode", MR: Major Response "≤2 emetic episode", MIR: Minor Response "3-5 emetic episode", TR: Treatment Failure "> 5 emetic episode".

6.6. Adherence to Guidelines

Adherence to MASCO guidelines was seen more in the treatment protocol of acute CINV (80%) while it was 28% in the treatment protocol of delayed CINV.

Nonadherence to guidelines due to the inappropriate dose, overprescription, underprescription and inappropriate selection of the drug were (n) 70%, 55%, 35%, and 0% in the treatment protocol of acute CINV while its due to inappropriate dose 4%, overprescription 33%, underprescription of drug 25% and inappropriate selection 65% of the treatment of delayed CINV.

6.6.1. Types of Nonadherence to Guidelines

Different types of nonadherence were detected in the study population in both acute and delayed CINV antiemetic protocols. The different forms were seen in Figure 6.3.

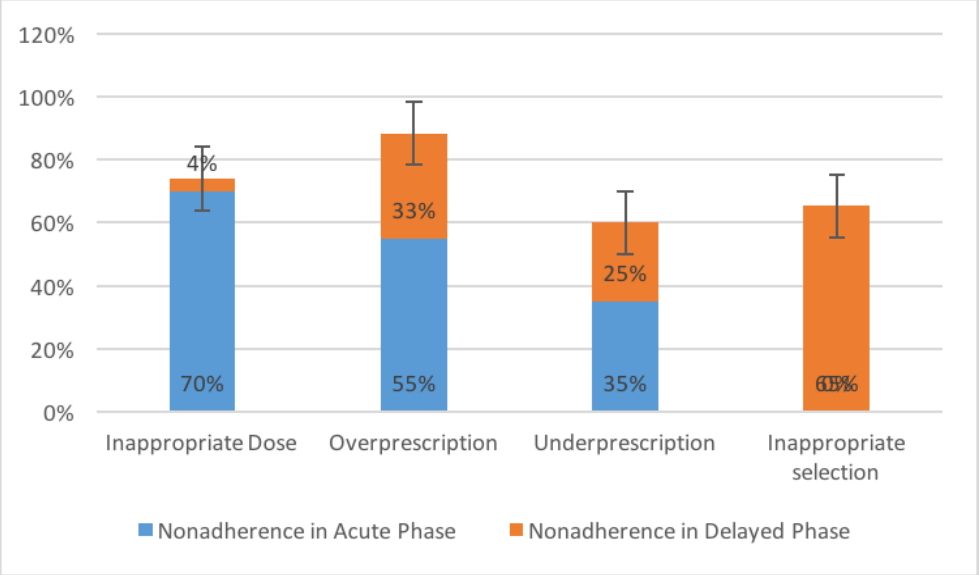

Figure 6.3. Types of Nonadherence to the Guidelines

6.6.2. Adherence to Guidelines and CINV

Adherence to guidelines have higher degree of complete control percentage in both acute and delayed management of chemotherapy induced nausea and vomiting as seen in Table 6.11.

Table 6.11. Impact of Adherence to Guidelines on Antiemetic Therapy Effectiveness

Chemotherapy cycle	Antiemetic Effect for acute CINV	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value
1ST	CC	70%	100%	<0.001*
	PR	10%	0%	
	MR	20%	0%	
2nd	CC	100%	98.8%	0.800
	PR	0%	0%	
	MR	0%	1.2%	
3rd	CC	100%	98.8%	0.800
	PR	0%	1.2%	
Chemotherapy cycle	**Antiemetic Effect for delayed**	**Nonadherence with guidelines for delayed CINV**	**Adherence with guidelines for delayed CINV**	**P value**
1st	CC	27.8	78.6%	0.005*
	CR	1.4%	0%	
	CP	5.6%	3.6%	
	PR	36.1%	3.6%	
	MR	11.1%	10.7%	
	MIR	9.7%	3.6%	
	TF	8.3%	0%	
2nd	CC	22.2%	85.7%	<0.001*
	CR	1.4%	0%	
	CP	2.8%	0%	
	PR	29.2%	0%	
	MR	37.5%	10.7%	
	MIR	6.9%	3.6%	
3rd	CC	26.4%	82.1%	0.004*
	CR	2.8%	0%	
	CP	1.4%	0%	
	PR	47.2%	10.7%	
	MR	19.4%	3.6%	
	MIR	2.8%	3.6%	

Table 6.11. Impact of Adherence to Guidelines on Antiemetic Therapy Effectiveness ***(Continiued)***

Chemotherapy cycle	Antiemetic Effect for delayed CINV	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value
1st	CC	91.7%	100%	0.132
	PR	2.8%	0%	
	MR	5.6%	0%	
2nd	CC	22.2%	85.7%	<0.001*
	CR	1.4%	0%	
	CP	2.8%	0%	
	PR	29.2%	0%	
	MR	37.5%	10.7%	
	MIR	6.9%	3.6%	
3rd	CC	98.6%	100%	0.720
	PR	1.4%	0%	

CC: Complete Control "no emetic episodes, no rescue therapy, and no nausea", CR: Complete Response "no emetic episodes, nausea likert scale 2 or less, rescue therapy", CP: Complete Protection "no emetic episode, no rescue therapy and no significant nausea likert scale 2 or less", PR: Partial Response "nausea with likert scale >2 and no emetic episode", MR: Major Response "≤2 emetic episode", MIR: Minor Response "3-5 emetic episode", TR: Treatment Failure "> 5 emetic episode".

6.7. Quality of Life

6.7.1 Reliability Test

The reliability test for the quality of life questionnaires was done and the Cronbach's alpha was 0.327 and 0.956 for FLIC and FLIE; respectively as shown in Table 6.12.

6.7.2 Quality of Life and Antiemetic Therapy Effectivness and Side Effects

A significant decrease in FLIE scores was seen after 5 days of chemotherapy as seen in Table 6.13. The difference in FLIE scores between adherence and nonadherence groups was seen in Table 6.14. The difference is statistically significant in the delayed phase, where Adherence to guidelines associated with higher FLIE score than nonadherence group. Table 6.15 described the relation between antiemetic effect and quality of life where decreased antiemetic effect has a low FLIE score. An increase in the intensity of side effects was associated with a significant decrease in the FLIE score as seen in Table 6.16**.**

Table 6.12. Reliability Test for Quality of Life Questionnaires

Questionnaire (n=100)	Mean	Variance	SD	Cronbach's alpha
FLIC (22-154)	93.82	123.46	± 11.1	0.327
FLIE (18-126)	1.77	0.428	± 30.7	0.956

FLIC: Functional living index cancer; FLIE: Functional living index emesis

Table 6.13. Patients FLIE Scores Before and After 5 Days of Chemotherapy

FLIE Questionnaire (n=100)	Mean	Median	SD	P value
Total score before chemotherapy	124	126	± 2.1	< 0.001*
Total score 5 days after chemotherapy	102.7	108	± 24.6	
Nausea domain	47.2	49.5	± 15.6	
Vomiting domain	55.6	63	± 12.6	

*p<0.05, Statistically significant at 95%

Table 6.14. Impact of Nonadherence to Guidelines on Functional Living Index Emesis Score

Prescription pattern for acute CINV	FLIE Scores Mean	FLIE Scores Median	SD	P value
Nonadherence with guidelines	97.4	102	± 22.2	0.099
Adherence with guidelines	104.1	109	± 25	
Prescription pattern for delayed CINV	**FLIE Scores Mean**	**FLIE Scores Median**	**SD**	**P value**
Nonadherence with guidelines	97.2	101.5	± 25.1	<0.001*
Adherence with guidelines	116.9	126	±15.9	

*p<0.05, Statistically significant at 95%

Table 6.15. Impact of Antiemetic Therapy Effectivness on FLIE Score

Chemotherapy cycles	Antiemetic effect	FLIE Score Mean	Median	SD	P value
Acute control CINV					
1st	CC	103	108	± 25.18	0.770
	PR	117	117	±1.4	
	MR	111	112.5	± 17.4	
2nd	CC	103.8	108	±24.7	0.283
	MR	80	80	0	
3th	No statistic				
Delayed control CINV					
1st	CR	107	107	0	<0.001*
	CP	104.8	108	± 17.9	
	CC	118.2	126	±20.4	
	PR	97.4	97	± 12.9	
	MR	92.2	89	±20.1	
	MIR	82.8	83	±23.4	
	TF	61.6	63	± 26.7	
2nd	CR	114	114	0	0.26080
	CP	63	63	0	
	CC	105.2	107.5	± 20.3	
	PR	96	104	± 26.9	
	MR	107	126	±26.8	
	MIR	104.8	122	±31	
3th	CR	120	120	±8.4	0.688
	CC	104.7	107	±19.9	
	PR	100.5	107.5	± 26.2	
	MR	106.4	123	± 31.4	
	MIR	101.6	126	± 42	

CC: Complete Control "no emetic episodes, no rescue therapy, and no nausea", CR: Complete Response "no emetic episodes, nausea likert scale 2 or less, rescue therapy", CP: Complete Protection "no emetic episode, no rescue therapy and no significant nausea likert scale 2 or less", PR: Partial Response "nausea with likert scale >2 and no emetic episode", MR: Major Response "≤2 emetic episode", MIR: Minor Response "3-5 emetic episode", TR: Treatment Failure "> 5 emetic episode".

Table 6.16. Impact of Side Effects severity on FLIE Score

Side effect	FLIE Score Mean	Median	SD	P value
Headache				
No headache	109	118.5	± 22.6	0.04*
Mild headache	97	96.5	± 21.8	
Moderate headache	98.75	100.5	± 28.3	
Severe headache	93	87	± 25	
Breathing difficulties				
No breathing difficulties	126	126	± 0	0.007*
Mild breathing difficulties	113.9	126	± 18.8	
Moderate breathing difficulties	101.3	107	± 24	
Severe breathing difficulties	91	93	± 29	
Sore throat				
No sore throat	104	108	± 23.4	0.043*
Mild sore throat	113.4	126	± 20.9	
Moderate sore throat	95	93	± 20.4	
Severe sore throat	69	71.5	± 39	
Vomiting				
No vomiting	116.6	126	± 15.5	0.025*
Mild vomiting	109.5	115.5	± 17.6	
Moderate vomiting	99.8	106	± 25.5	
Severe vomiting	84.2	79.5	± 30.7	

6.8 Side Effects

Many side effects were recorded by patients, the frequency and severity of side effects were seen in Table 6.17. The nonadherence with guidelines was associated with a higher incidence of having diarrhea, headache, nausea, swallowing problems and dark coloured stool ($p < 0.05$)

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Joint pain						
no	60%	43,8%	0.810	47.2%	46.4%	0.577
Mild	5%	23.8%		19.4%	21.4%	
Moderate	20%	25%		20.8%	32.1%	
Severe	15%	7.5%		12.5%	0%	
Back pain						
No	60%	55%	0.960	59.7%	46.4%	0.286
Mild	15%	20%		19.4%	17.9%	
Moderate	15%	18.8%		12.5%	32.1%	
Severe	10%	6.2%		8.3%	3.6%	
Myalgia						
No	55%	53.8%	0.480	52.8%	57.1%	0.293
Mild	5%	20%		15.3%	21.4%	
Moderate	30%	21.2%		23.6%	21.4%	
Severe	10%	5%		8.3%	0%	
General weakness						
No	25%	20%	0.365	19.4%	25%	0.158
Mild	15%	12.5%		12.5%	14.3%	
Moderate	40%	35%		31.9%	46.4%	
Severe	20%	32.5%		36.1%	14.3%	
Abdominal pain						
No	55%	58.8%	0.885	51.4%	75%	0.065
Mild	20%	15%		19.4%	7.1%	
Moderate	15%	17.5%		18.1%	14.3%	
Severe	10%	8.8%		11.1%	3.6%	
Constipation						
No	55%	49.4%	0.613	50%	51.9%	0.909
Mild	15%	21.5%		19.4%	22.2%	
Moderate	25%	15.2%		19.4%	11.1%	
Severe	5%	13.9%		11.1%	14.8%	
Diarrhea						
No	70%	68.8%	0.855	63.9%	82.1%	0.044
Mild	15%	18.8.%		19.4%	14.3%	*
Moderate	15%	7.5%		11.1%	3.6%	
Severe	0%	5%		5.6%	0%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Headache						
No	45%	51.2%	0.783	41.7%	71.4%	0.035*
Mild	20%	17.5%		20.8%	10.7%	
Moderate	25%	18.8%		25%	7.1%	
Severe	10%	12.5%		12.5%	10.7%	
Bloating						
no	90%	80%	0.396	81.9%	82.1%	0.944
mild	5%	6.2%		6.9%	3.6%	
moderate	0%	11.3%		6.9%	14.3%	
severe	5%	2.5%		4.2%	0%	
Nausea						
no	40%	45%	0.965	34.7%	67.9%	0.002*
mild	25%	21.2%		22.2%	21.4%	
moderate	25%	16.3%		23.6%	3.6%	
severe	10%	17.5%		19.4%	7.1%	
Swallowing problems						
no	75%	67.5%	0.675	62.5%	85.7%	0.017*
mild	10%	10%		11.1%	7.1%	
moderate	5%	17.5%		18.1%	7.1%	
severe	10%	5%		8.3%	0%	
Vomiting						
no	65%	71.2%	0.905	68.1%	75%	0.236
mild	20%	15%		15.3%	17.9%	
moderate	15%	8.8%		11.1%	7.1%	
severe	0%	5%		5.6%	0%	
Dyspepsia						
no	55%	52.5%	0.650	50%	60.7%	0.085
mild	15%	21.2%		18.1%	25%	
moderate	15%%	21.2%		22.2%	14.3%	
severe	15%	5%		9.7%	0%	
Dark coloured stools						
no	70%	76.2%	0.665	68.1%	92.9%	0.013*
mild	10%	8.8%		11.1%	3.6%	
moderate	20%	12.5%		18.1%	3.6%	
severe	0%	2.5%		2.8%	0%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Gingival bleeding						
no	80%	80%	0.717	80.6%	78.6%	0.846
mild	15%	12.5%		12.5%	14.3%	
moderate	5%	3.8%		4.2%	3.6%	
severe	0%	3.8%		2.8%	3.6%	
Frequent urination						
no	50%	52.5	0.897	50%	57.1%	0.763
mild	15%	12.5%		16.7%	3.6%	
moderate	25%	18.8%		20.8%	17.9%	
severe	10%	16.2%		12.5%	21.4%	
Hematuria						
no	95%	93.8%	0.568	93.1%	96.4%	0.684
mild	5%	2.5%		4.2%	0%	
moderate	0%	2.5%		1.4%	3.6%	
severe	0%	1.2%		1.4%	0%	
Painful urination						
no	65%	76.2%	0.744	72.2%	78.6%	0.727
mild	25%	12.5%		16.7	10.7%	
moderate	10%	7.5%		8.3%	7.1%	
severe	0%	3.8%		2.8%	3.6%	
Dark colored urine						
no	60%	75%	0.401	66.7%	85.7%	0.166
mild	25%	11.2%		16.7%	7.1%	
moderate	10%	10%		12.5%	3.6%	
severe	5%	3.8%		4.2%	3.6%	
Reduction in amount of urine						
no	85%	70%	0.484	72.2%	75%	0.412
mild	0%	13.8%		9.7%	14.3%	
moderate	10%	12.5%		12.5%	10.7%	
severe	5%	3.8%		5.6%	0%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Fatigue						
no	40%	35%	0.695	38.9%	28.6%	0.452
mild	15%	18.8%		16.7%	21.4%	
moderate	30%	26.2%		26.4%	28.6%	
severe	15%	20%		18.1%	21.4%	
Somnolence						
no	45%	43.8%	0.819	37.5%	60.7%	0.132
mild	20%	20%		23.6%	10.7%	
moderate	25%	22.5%		25%	17.9%	
severe	10%	13.8%		13.9%	10.7%	
Drowsiness						
no	55%	46.2%	0.323	47.2%	50%	0.218
mild	20%	17.5%		13.9%	28.6%	
moderate	20%	25%		26.4%	17.9%	
severe	5%	11.2%		12.5%	3.6%	
Amnesia						
no	75%	71.2%	0.898	70.8%	75%	0.175
mild	15%	18.8%		15.3%	25%	
moderate	5%	6.2%		8.3%	0%	
severe	5 %	3.8%		5.6%	0%	
Balance disorder						
no	90%	63.8	0.091	63.9%	15.3%	0.232
mild	0%	15%		15.3%	3.6%	
moderate	5%	12.5%		12.5%	7.1%	
severe	5%	8.8%		8.3%	7.1%	
Loss of appetite						
no	55%	52.5	0.654	48.6%	64.3%	0.066
mild	20%	17.5%		16.7%	21.4%	
moderate	15%	15%		18.1%	7.1%	
severe	10%	15%		16.7%	7.1%	
Tremor						
no	75%	63.8%	0.488	62.5%	75%	0.520
mild	15%	15%		16.7%	3.6%	
moderate	15%	11.2%		11.1%	14.3%	
severe	5%	10%		9.7%	7.1%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Thirstiness			0.880			0.648
no	70%	61.2%		62.5%	64.3%	
mild	5%	15%		12.5%	14.3%	
moderate	15%	17.5%		16.7%	17.9%	
severe	10%	6.2%		8.3%	3.6%	
Depression						
no	80%	61.2%		62.5%	71.4%	0.933
mild	5%	16.2%	0.156	16.7%	7.1%	
moderate	15%	15%		16.7%	10.7%	
severe	0%	7.5%		10.7%	10.7%	
Photophobia						
no	70%	63.8%		68.1%	57.1%	0.755
mild	10%	15%	0.503	9.7%	25%	
moderate	20%	12.5%		15.3%	10.7%	
severe	0%	8.8%		6.9%	7.1%	
Stress						
no	70%	51.2%	0.123	55.6%	53.6%	0.386
mild	10%	18.8%		20.8%	7.1%	
moderate	20%	18.8%		15.3%	28.6%	
severe	0%	11.2%		8.3%	10.7%	
Confusion						
no	65%	61.2%	0.912	61.1%	64.3%	0.188
mild	10%	21.2%		15.3%	28.6%	
moderate	25%	11.2%		16.7%	7.1%	
Severee	0%	6.2%		6.9%	0%	
Loss of concentration						
no	85%	72.5	0.481	73.6%	78.6%	0.479
mild	0%	13.8%		11.1%	10.7%	
moderate	15%	11.2%		12.5%	10.7%	
severe	0%	2.5%		2.8%	0%	
Vulnerability						
no	90%	72.2%	0.173	75%	77.8%	0.923
mild	5%	20.3%		18.1%	14.8%	
moderate	5%	6.3%		6.9%	3.7%	
severe	0%	1.3%		0%	3.7%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Breathing difficulties						
no	80%	65%	0.455	68.1%	67.9%	0.830
mild	5%	17.5%		15.3%	14.3%	
moderate	10%	13.8%		11.1%	17.9%	
severe	5%	3.8%		5.6%	0%	
Cough						
no	80%	68.8%	0.337	72.2%	67.9%	0.783
mild	10%	12.5%		11.1%	14.3%	
moderate	5%	11.2%		9.7%	10.7%	
severe	5%	7.5%		6.9%	7.1%	
Sore throat						
no	70%	75%	0.554	69.4%	85.7%	0.140
mild	10%	11.2%		12.5%	7.1%	
moderate	15%	10%		13.9%	3.6%	
severe	5%	3.8%		4.2%	3.6%	
Flu						
no	90%	73.8%	0.599	77.8%	75%	0.748
mild	0%	20%		13.9%	21.4%	
moderate	5%	5%		5.6%	3.6%	
severe	5%	1.2%		2.8%	0%	
Sneezing						
no	80%	71.2%	0.338	73.6%	71.4%	0.865
mild	20%	25%		22.2%	28.6%	
moderate	0%	3.8%		4.2%	0%	
severe	0%	0%		0%	0%	
Itching						
no	95%	84.8%	0.299	86.1%	88.9%	0.42
mild	0%	6.3%		6.9%	0%	
moderate	5%	5.1%		6.9%	0%	
severe	0%	3.8%		0%	11.1%	
Dry skin						
no	80%	70%	0.216	73.6%	67.9%	0.137
mild	15%	13.8%		15.3%	10.7%	
moderate	5%	12.5%		11.1%	10.7%	
severe	0%	3.8%		0%	10.7%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Swelling						
no	80%	70%	0.321	68.1%	82.1%	0.155
Mild	5%	10%		8.3%	10.7%	
moderate	15%	11.2%		16.7%	0%	
Severe	0%	8.8%		6.9%	7.1%	
Red skin rash						
No	100%	65%		69.4%	78.6%	0.239
Mild	0%	16.2%	0.006*	12.5%	14.3%	
moderate	0%	11.2%		11.1%	3.6%	
Severe	0%	7.5%		6.9%	3.6%	
Occular pain						
No	95%	85%	0.722	86.1%	89.3%	0.899
Mild	0%	11.2%		9.7%	7.1%	
moderate	0%	2.5%		2.8%	0%	
Severe	5%	1.2%		1.4%	3.6%	
Visual impairment						
No	85%	80%	0.416	77.8%	89.3%	0.231
Mild	10%	8.8%		9.7%	7.1%	
moderate	5%	7.5%		9.7%	0%	
Severe	0%	3.8%		2.8%	3.6%	
Palpitation						
No	85%	82.5%	0.948	83.3%	82.1%	0.699
Mild	5%	7.5%		6.9%	7.1%	
moderate	5%	6.2%		6.9%	3.6%	
Severe	5%	3.8%		2.8%	7.1%	
Fever						
No	80%	77.5%	0.909	76.4%	82.1%	0.306
Mild	0%	7.5%		4.2%	10.7%	
moderate	15%	10%		13.9%	3.6%	
Severe	5%	5%		5.6%	3.6%	
Tinnitus						
No	85%	55%		58.3%	67.9%	0.586
Mild	10%	21.2%	0.016*	20.8%	14.3%	
moderate	5%	21.2%		19.4%	14.3%	
Severe	0%	2.5%		1.4%	3.6%	

Table 6.17. Impact of Nonadherence to Guidelines on Side Effects Frequency ***(Continiued)***

Side Effect	Nonadherence with guidelines for acute CINV	Adherence with guidelines for acute CINV	P value	Non adherence with guidelines for delayed CINV	Adherence with guidelines for delayed CINV	P value
Hot flushes						
No	100%	72.5%	0.014*	80.6%	71.4%	0.278
Mild	0%	18.8%		13.9%	17.9%	
moderate	0%	8.8%		5.6%	10.7%	
severe	0%	0%		0%	0%	
Pallor						
No	95%	87.5%	0.278	88.9%	89.3%	0.516
Mild	5%	7.5%		5.6%	10.7%	
moderate	0%	3.8%		4.2%	0%	
severe	0%	1.2%		1.4%	0%	
Nose bleed						
no	100%	93.8%	0.276	93.1%	100%	0.174
mild	0%	2.5%		2.8%	0%	
moderate	0%	3.8%		4.2%	0%	
severe	0%	0%		0%	0%	

6.9. Drug-Drug Interaction

6.9.1 Drug-Drug Interactions Frequency

The frequency of drug interaction was showen according to its significance in Figure 6.4. Sixty-one percent of the population has drug interactions categorized as 55%, 5%, 1% for significant, minor and serious respectively as seen in Figure 6.4.

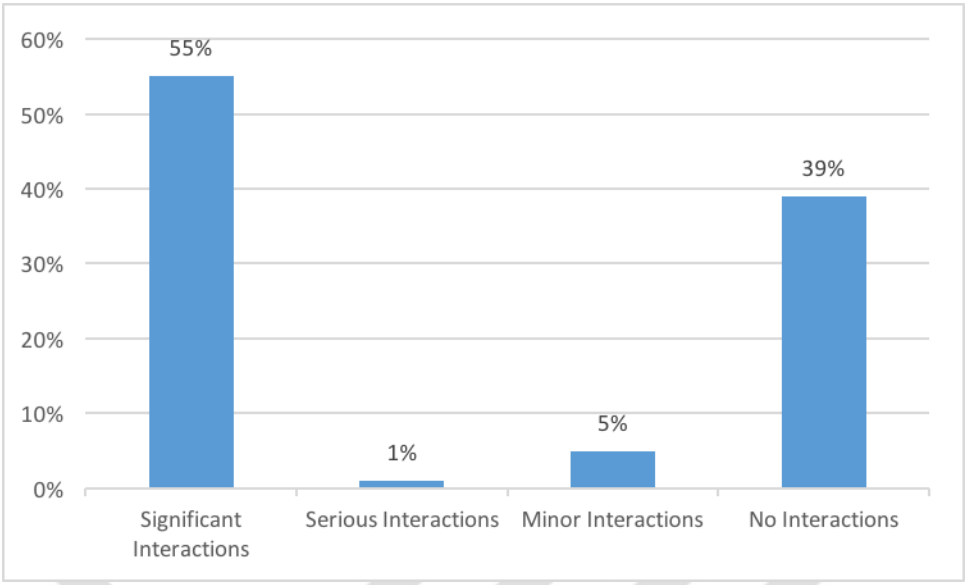

Figure 6.4. Drug Interactions Frequency (n=100)

6.9.2. Nonadherence to Guidelines and Drug and Drug Interactions

There are no differences in term of drug interactions between groups of adherence and nonadherence to guidelines ($p>0.05$).

6.9.3. Quality of Life and Drug Interactions

There are no significant differences in FLIE scores between different drug interactions categories ($p>0.05$).

6.9.4. Drug Interaction Types

In a total of 61% drug interaction were reported of those 55% was considered as significant occured mostly between aprepitant and dexamethasone, dexamethasone and paclitaxel, dexamethasone and doxorubicin ,1% serious occurred between dexamethasone + irinotecan and 5% minor like dexamethasone and docetaxel. Figure 6.5, 6.6 describes the significant and minor drug interactions that were seen in the study population.

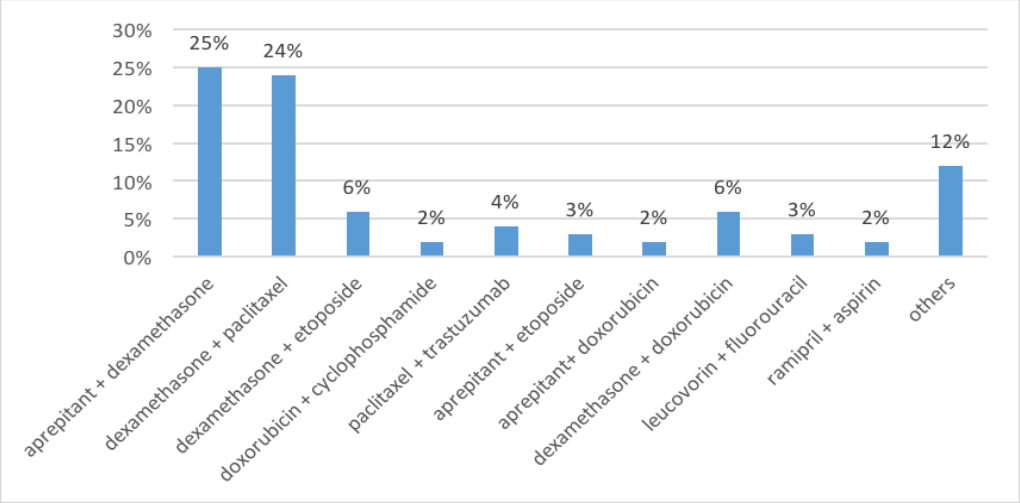

Figure 6.5. Significant Drug Interaction

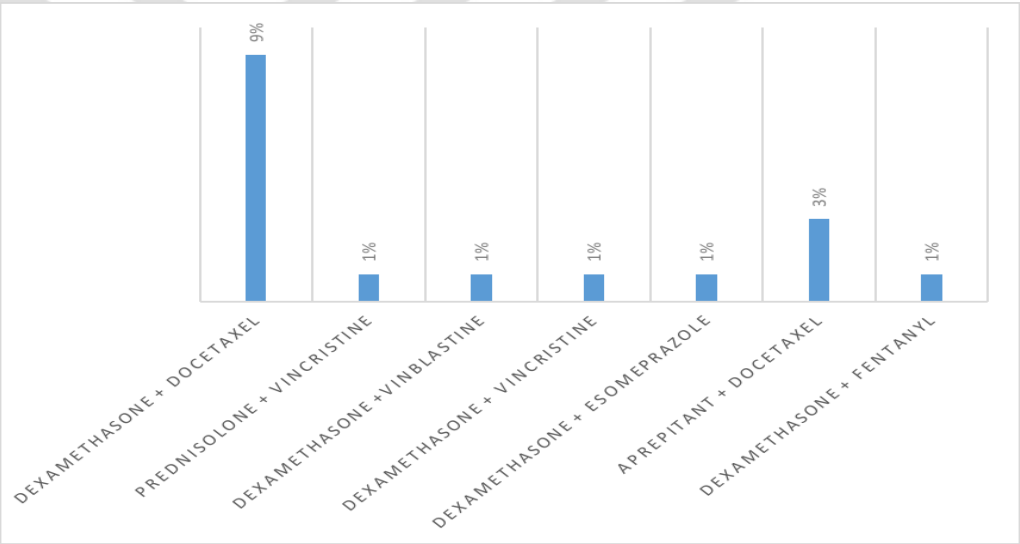

Figure 6.6. Minor Drug Interactions

The relation between the number of medications and the drug drug interaction is seen in Table 6.18. It can be seen that drug interaction incidence increased with increase number of medications.

Table 6.18. Drug Interaction and the Number of Medications

Drug Interaction	Number of medication Mean	Median	SD	P value
Minor interaction	6	7	± 2	<0.001*
Significant interaction	7.2	8	± 0.97	
Serious interaction	5	5	± 0	
No interaction	4.2	4	± 0.48	

*p<0.05. Statistically significant at 95%

6.10 Patient Education

Six percent of patients do not receive any information about their medications neither from the health care providers in the hospital nor from the pharmacist who dispense the medication in pharmacy.

6.10.1 Patient Education and Antiemetic Therapy Effectivness

Patients who received adequate patient education from the health care providers (physician or nurse) have more complete control to nausea and vomiting. The difference was significant during the three chemotherapy cycles as seen in Table 6.19.

Table 6.19. Impact of Patient Education on t Antiemetic Therapy Effectivness

Chemotherapy cycle	Education	Antiemetic drug effect for delayed CINV							P value
1st		CR	CP	CC	PR	MR	MIR	TF	
	Patient education	1	5	42	27	11	8	0	<0.001*
	No patient education	0	0	0	0	0	0	6	
2nd	Patient education	1	2	40	21	25	5	0	0.004*
	No patient education	0	0	0	0	5	1	0	
3rd	Patient education	2	1	42	35	12	2	0	0.002*
	No patient education	0	0	0	2	3	1	0	

CR: complete response; CP: Complete protection; CC: Complete Control; PR: partial response; MR: major response; MIR: minor response; TF: treatment failure

7. DISCUSSION and CONCLUSION

Lately, many new antiemetic drugs which prevent 70-80% of chemotherapy-induced vomiting have been discovered. The control of nausea is still insufficient and elicits the serious drawback of distrust in cancer patients worldwide. Control of CINV depends on many factors which must be standardised to obtain optimal results. The utilisation process should be closely monitored from the antiemetic prescription until its administration. Irrational uses of medication should be eradicated before introducing more expensive and unnecessary medication to hospital formulas. Rational drug use involves the administration of the correct drug to the right patient at the right doses and times. The decline of drug effectiveness is an inevitable result of irrational drug use. Pharmaceutical care plan must be developed to ensure rational use of antiemetic therapy and optimization of palliative care. In order to develop this plan the pharmaceutical needs for these population must be identifed and clarifed. In this study we observed the prescreption process of antiemetic drugs, side effect, drug drug interactions, quality of life to determine these needs.

According to the study results, guidelines adherence was observed more with acute than with delayed treatment of CINV, 80% and 28%; respectively. While adherence with guidelines were associated with 100% and 78.6% complete control, the complete control was achieved only in 70% and 27.8% in nonadherence of acute and delayed CINV; respectively. The significance was ceased in the second and the third cycle for acute phase while it continued in the second and the third cycle of the delayed phase ($p< 0.001$ and $p=0.004$ respectively). Side effects like headache and swallowing problems, diarrhea and dark coloured stool were significantly seen in guidelines nonadherence group with delayed CINV management, while hot flushes, tinnitus and red coloured skin were more significantly seen in adherence group for acute CINV management. Significant differences in quality of life scores were noticed between the groups of adherence with guidelines associated with higher quality of life scores. Drug - drug interactions were detected in 61% of the prescriptions, distributed as 1%, 55%, 5% for serious, significant and minor drug interactions respectively. The major source of significant interactions was the

interactions between the supportive therapy itself and also between supportive therapy and chemotherapy agents.

Demographic variables for the patients were assessed and the effect of these variables on the efficacy of antiemetic medications that prescribed to the patients were also evaluated. The difference is significant only in young age group where vomiting is seen more at the group of <55 years old. This result was expected as the incidence of nausea and vomiting is the highest at this age group in many clinical trials (Pollera and Giannareli, 1989; Pater et al., 1994; Schnell, 2003; Bajetta et al.,2009; Sekine et al., 2013). Although this difference is appeared significantly in the first cycle, it disappears within time so age differences did not affect the drug efficacy in the following cycles. Although female patients has a higher incidence for nausea and vomiting in many studies (Schnell, 2003), there is no significant differences was seen between male and female on the efficacy of antiemetic drug in our study.

Most patients have previous history of smoking and alcohol consumptions but patients denied that they continue smoking and alcohol consumption during the treatment and this may explain the absence of significant difference in CINV between smokers, alcoholic and nonsmoker, nonalcoholic. Studies that were done to evaluate the effect of alcohol and smoking on the emesis showed that in patients who consume >10 alcohol unit/week and smoke, have lower incidence of CINV (Bajetta et al.,2009).

Marital status did not display any differences in patients' tendency to develop CINV and this result is compatible with the results from other studies (de Boer-Dennert., 1997)

Although educational levels show some differences in antiemetic effect, these differences were not significant. Educational level may have some correlation to anticipatory nausea and vomiting more than for acute or delayed CIN (Ruzsa et al.,2013).

Although patient population include different cancer types, these types did not affect the incidence of chemotherapy induced nausea and vomiting. Studies that were

done to determine the incidence of chemotherapy induced nausea and vomiting did not found any direct association with cancer type but it correlate with the advanced stage of cancer. The high incidence of CINV due to Malignant Bowel Obstruction (MBO) of the gastrointestinal tract which is a common complication of advanced cancer, especially in patients with bowel or gynecological cancer. These include colorectal cancer, ovarian cancer, breast cancer and melanoma (Ripamonti et al., 2008). Three percent of all advanced cancers lead to malignant bowel obstruction and 25 to 50 percent of patients with ovarian cancer experience at least one episode of malignant bowel obstruction (Glare et al., 2011). The mechanisms of action that may lead to nausea in MBO include mechanical compression of the gut, motility disorders, gastrointestinal secretion accumulation, decreased gastrointestinal absorption and inflammation. Unfortunately, information about the Cancer stage is deficient, such information is not presented in most of the patient profiles, therefore it is difficult to make any comment on this observation.

In our study, certain comorbidity was seen in patient's population (29%). Diabetes mellitus, congestive heart failure, hypertension were the most seen comorbidity. Although reflux was seen in some patients, but the severity of reflux is very mild. There are no significant differences in CINV in the presence or absence of comorbidity. Studies that have been done in oncology patients showed that comorbidities will increase the number of medications received and combined with a potential decline in liver and renal functions resulting in increased drug drug interactions and side effects (Jörgensen et al.,2001; Jakobsen and Herrstedt, 2009). There are no correlations between comorbidities and incidence of drug drug interactions and side effects seen in our study.

Laboratory tests are used as a routine test to exclude other causes for nausea and vomiting and determines its consequences. Complete blood count required to exclude leukocytosis in an inflammatory process, microcytic anemia from a mucosal process and electrolyte to assess consequences of nausea and vomiting (e.g. acidosis. Alkalosis, azotemia, hypokalemia), ALT, AST, Gama Glutamyl Transferase GTT, urea, creatinine, uric acid and creatinine clearance to exclude any hepatic or renal causes of nausea and vomiting (Scorza et al., 2007).

In our study all the laboratory test results were normal and indicated the absence of any extra causes of nausea and vomiting in the population and the correlation tests prohibit any correlation between laboratory test results and nausea and vomiting. According to these results any nausea and vomiting recorded will be due to chemotherapy effect.

The study population includes patients who receive high, moderate and mild emetogenic chemotherapy protocol. The level of emetogencity was determined using MASCC guidelines as seen in (Appendix 9). The emetogenic level is determined by identifying the most emetogenic agent in the combination and then assessing the relative contribution of the other agents (Basch et al., 2011; Roila et al., 2010). Cisplatin and cyclophosphamide + doxorubicin combination were the most frequently seen high emetogenic protocol in our study. After treatments were given the differences between these different protocol disappears and the level of emetogencity play no role in determination of antiemetic efficacy.

Four different duration of chemotherapy cycle were seen in this study 7, 14, 21 and 28 days. There is no difference in the incidence of CINV and the efficacy of antiemetic drug between the different chemotherapy cycle lengths. The studies confirm that multiday regimens were seen to be more challenging than single day regimens as patients are at risk for acute CINV each day of chemotherapy (Affronti et al., 2014) but the differences in the duration of chemotherapy cycle were not involved in any study.

A significant nonadherence to the guidelines was detected in both acute and delayed CINV protocols. The deviation has different forms such as inappropriate dose, inappropriate selection, overprescription or underprescription of antiemetic drug.

Inappropriate dose was the main cause for nonadherence in the acute phase of CINV where dexamethasone was given as 16 mg i.v. prior to chemotherapy for all the patients regardless to the addition of aprepitant or $5HT_3$ antagonists for high emetogenicity risk patients. According to MASCC guidelines the dose of dexamethasone differs according to the emetogenicity potential where the dose of 20,

12, 8, 4-8 mg for high, high with aprepitant, moderate, low emetogenic risk and respectively for acute prevention of CINV (MASCC 2014). The 16 mg dose was not tested in any of the largest randomized trials that attempted to measure the most effective dose of dexamethasone while other doses of 20, 12, 8 mg were frequently tried. The Italian Group examined the most effective dose of dexamethasone given concomitantly with 8 mg ondansetron (n=531) in patients receiving HEC (cisplatin $\geq$50 mg/m^2). The result showed a complete protection achieved in 83% and 71% for vomiting and nausea respectively in patients receiving 20 mg dexamethasone (the highest dose) compared with the other doses (Italian Group, 1998). The concomitant use of aprepitant with dexamethasone resulted in significant increase in the blood concentration of the latter, AUC_{0-24} increased 2.2 fold ($p<0.01$), this interaction is mediated through the aprepitant moderate inhibitory effect for P4503A4 (McCrea et al., 2003). Depending on these pharmacokinetic interaction, the dose of dexamethasone was decreased from 20 mg to 12 mg when combined with aprepitant for the prevention of acute CINV in all the clinical trials (Hesketh, 2003; Poli-Bigelli et al., 2003; Warr et al., 2005). An inappropriate dose is caused for 4% of GNGD, in the study patients received 8 mg dexamethasone twice daily for three to four days for the prevention of delayed CINV regardless of aprepitant used in the second and third day. The dose of dexamethasone must be decreased from 8 mg twice daily to 8 mg once daily, for the second and third day when administered concomitantly with aprepitant (Hesketh, 2003; Poli-Bigelli et al., 2003; Warr et al., 2005).

In appropriate selection; this form of deviation was more pronounced with the antiemetic protocol for delayed nausea and vomiting. Mainly all the patients received $5HT_3$ receptor antagonists 'granisetron' regardless to the emetogenicity level of chemotherapy. Although some benefit has been seen when $5HT_3$ antagonists used as monotherapy, the benefit has not been as great as that seen with glucocorticoids (Olver et al., 1996; Navari et al., 1995; Goedhals et al., 1998; Geling and Eichler, 2005). The use of $5HT_3$ receptor antagonist as a sole maneuver to prevent delayed emesis in patients receiving cisplatin is not recommended. Even if $5HT_3$ receptor antagonists have to be used, the second generation $5HT_3$ receptor antagonist palonosetron seem to be superior to other $5HT_3$ receptor antagonists for the treatment of delayed emesis due to cisplatin-based chemotherapy. Palonosetron 0.25 mg was

superior to ondansetron for control of delayed and overall emesis in patients receiving concomitant dexamethasone (Aapro et al., 2006; Saito et al., 2009).

In this study over prescription for granisetron was noticed mostly in patient receiving low emetogenic chemotherapy. A combination therapy of dexamethasone and granisetron was given, while guidelines recommend use of single agent to control acute CINV. The over prescription of antiemetic in patients receiving LEC was noticed in many studies. In a survey conducted at a cancer center in Singapore to assess the prescription pattern of antiemetic drugs, the prescriptions of twenty-seven oncologists were assessed. Over prescription of antiemetic for patients receiving LEC were confirmed (Chan et al.,2008).

Under prescription of palonosetron and dexamethasone was also noticed in both GNGA, GNGD; respectively. MASCC guidelines recommended palonosetron – dexamethasone combination for CINV prevention in patients receiving MEC. MASCC recommendations depend on evidence that second generation $5HT_3$ palonosetron was more effective than first generations drugs for acute CINV prevention in patients receiving MEC (Gralla, 2003; Eisenberg et al., 2003; Likun et al., 2011). Under prescription of dexamethasone is characterized in GNGD. The lack of dexamethasone use in day two and three of post chemotherapy was the most frequent type of nonadherence to antiemetic guidelines in a study that observed sixty one patients with colorectal cancer receiving MEC (Fujii et al., 2013). The same result was confirmed in a study conducted by King Saud University in Saudi Arabia. Antiemetic prescriptions for one hundred and fifty five patients were assessed and the results showed that granisetron was used in twice the recommended doses in 87.7%, granisetron and metoclopromide overuse was 16%, 62.6% respectively, underuse of dexamethasone was 27% and corticosteroids were duplicated in 7.7%, for the prechemotherapy treatment for nausea and vomiting while overuse of granisetron and metaclopromide 81.9% and 34.2% respectively and underuse of dexamethasone 66.5% for post chemotherapy medications (Almazrou, 2012).

In this study, adherence with the guideline was seen more in acute than in the delayed prevention of CINV (80% vs 28% respectively). In this study, health care professionals were more concerned with the acute prevention. There are significant

differences between both GAG and GNG. A complete control was achieved in 100%, 70% for GAGA, GNGA; respectively and in 78.6%, 27.8% for GAGD, GNGD; respectively (complete control; no vomiting episodes, no breakthrough therapy and no nausea). While these significant differences disappeared in the second and the third chemotherapy cycles of the acute prevention, these differences persisted for the second and third cycles for the delayed control of CINV. This result was expected as the international guidelines are standard guidelines that depend on strong evidence based on very robust clinical trials.

Many studies evaluate the effect of guideline adherence on the emetic control. A large European observational study (n=1000) showed that patients receiving guideline-consistent antiemetic prophylaxis had significantly better CINV control than those who did not receive guideline-consistent treatment (CR rates 60% vs 51%. respectively; p = 0.008) (Aapro et al., 2012). Gilmore et al, studied the impact of consistency with guidelines in US oncology practices (n= 1295), the cohort study was multicentered. The result showed that the incidence of CINV in guideline consistent cohort group (GCCP) was significantly lower than in guideline inconsistent cohort group (GICP) $p<0.001$(Gilmore et al., 2014). Although our study has a small sample size in comparison with the Aapro and Glimore studies, it confirmed the necessity to follow guidelines. In our study significant differences in prevalence of headache, diarrhea, swallowing problem and dark colored stool between GAGD and GNGD were seen with the later associated with higher prevalence. These side effects were the main side effects of $5HT_3$ antagonist and the over prescription of $5HT_3$ in the prevention of delayed CINV may explain its high prevalence in GNGD (Goodin and Cunningham, 2002).

Functional Living Index Cancer (FLIC) is a questionnaire that has been used to measure the quality of life in oncology patients. This questionnaire was validated in Turkey. The 22 items questionnaire of theTurkish version was administered to 110 cancer patients who had been receiving chemotherapy. The Cronbach alpha reliability for the total scale was 0.88 (Bektas and Akdemir, 2008). Depending on this data, the questionnaire was administered to the 100 patients in our study but the Cronbach's alpha was 0.327, this means the reliability of the test is very low and data

extracted from this questionnaire cannot be used as a reference for quality of life assessment for those patients. A decreased reliability of this questionnaire may be due to miss understanding of longquestions as 65% of the study population were graduated from elementary school or illiterate, which makes it difficult to understand, therefore revalidation of FLIC items in this population must be considered.

The Turkish version of Functional Living Index Emesis (FLIE) were used to evaluate the effect of CINV on the patient's quality of life; the questionnaire contains 18 specific short items which make it easy to be administered (Aksu et al., 2013). The reliability test was done; Cronbach's alpha was 0.956 which means the quality of life information extracted from this questionnaire were highly reliance.

A decrease in mean FLIE score was observed (124 to 102.7), and it indicated that nausea and to a lesser extent vomiting (47.2, 55.6) substantively influenced patient ability to complete household tasks, enjoy meals, spend time with family and friend and maintain daily function and recreation. Although there are no significant differences in FLIE scores between nonadherence and adherence groups for acute CINV, significanct difference in FLIE score with p value <0.001 were noticed for delayed CINV. The FLIE score is lower for patients received antiemetic therapy nonadherent with guidelines. This result might indicate that nonadherence with guidelines associated with high incidence of nausea which affects the patient's quality of life. ANOVA test also supported the hypothesis that a good control of nausea and vomiting significantly contributes to increased FLIE score where complete control for delayed chemotherapy induced nausea and vomiting associated with higher scores. The effect of adherence with guidelines on patient's quality of life was not studied before, but these effects may be directly related to the fact that adherence with guidelines is associated with less nausea and vomiting. An evaluation of the relationship between nausea and vomiting and patient's quality of life has started when Meyerowitz et al studied the quality of life for 50 women receiving adjuvant chemotherapy for stage II breast cancer. In Meyerowitz's study 88%, 28% of these women develop nausea and vomiting respectively and both nausea and vomiting have a major disruptive influence on the patient quality of life (Meyerowitz

et al., 1979). This study assessed only physical domains of quality of life, other studies used FLIE to assess the patient quality of life on multiple dimensions (physical, psychological and social function) and the decline in FLIE scores indicated that patients experienced acute decline in their quality of life during the immediate treatment period (Lindley and Hirsch, 1992 ; Bloechl-Daum B et al., 2006; Ballatori et al., 2007; Cohen et al., 2007; Fernández-Ortega et al., 2012). The effect of adherence with guidelines on patient's quality of life not studied before in the literature or in Turkey.

Some side effects such as headache, breathing difficulties and sore throat, their severity were associated with decline in FLIE scores. These side effect can be related to the use of $5HT_3$ receptor antagonists such as granisetron or it can be direct side effect of chemotherapy.

There are significant differences in the incidence of some side effects between adherence and nonadherence groups, where tinnitis, hot flushes and red skin rashes were seen more with adherence with acute CINV management guidelines. Precise explanation can not be done and direct correlation with the chemotherapy that used or the antiemetic drug can't be created, However, it is assumed that adherent group contains a patient having vincristine, which may be accounted for increase incidence of tinnitis. Significant differences have also seen in the incidence of other side effects like headache, diarrhea, nausea, swallowing problems, dark colored stools, therefore it is difficult to emphasize the exact correlation with chemotherapy or antiemetic drugs.

Anticancer agents have narrow therapeutic index and inherent toxicity which makes drug interactions very important and critical issue for oncology patients. Drug interactions can alter drug's efficacy or toxicity by causing small changes in the pharmacokinetics or pharmacodynamic of a chemotherapy agent.

A drug interaction is defined as the pharmacological or clinical response to the administration or co-exposure of a drug with another substance that modifies the patient's response to the drug. It is reported that 20-30% of all adverse reactions to drugs are caused by interactions between drugs (Kuhlmann and Mück, 2001).

Drug interactions that identified in our study include interactions between chemotherapy- chemotherapy, chemotherapy–supportive therapy and chronic therapy for comorbidities-supportive therapy.

Fifty-five of the study population have significant drug interactions in which monitoring by health care provider is likely required. Serious drug interactions defined as "require regular monitoring by healthcare provider or alternate medication may be needed" is seen very rarely in 1% of the patients, the remaining drug interactions were minor drug interactions which is considered as nonsignificant and require no intervention. Many articles describe the incidence of drug-drug interactions (DDIs) in oncology population, some of these studies used electronic methods to screen for potential DDIs others carried out in a single institution like our study, the frequency of the potential drug interactions in these trials range between 12-81% which is consistent with our study.

A Norwegian study found that severee drug interaction may be the leading cause of 4% of cancer related death in hospitalized patients (Buajordet et al., 2001). In our study we could not approve the relation between drug interactions and mortality rate.

A significant correlation was seen between number of medication that patients received and the incidence of drug-drug interactions which is consistent with previous studies (Geppert et al., 2003; Herr et al., 1992; Beers et al.,1990; Riechelmann et al., 2007) .

Pharmacokinetic studies showed that the plasma concentration of dexamethasone therapeutic dose that used for CINV prevention is increased when drug is coadministered with aprepitant. The increase was approximately two fold and most likely involves the inhibition of CYP3A4 by aprepitant. The dose of dexamethasone should be adjusted when it is given with aprepitant (McCrea et al., 2003; Takahashi et al., 2011); the dose must be reduced from 20 mg to 12 mg on day1 and from 8 mg twice daily to 8 mg daily on day 2 and 3 (Hesketh et al., 2003; de Wit, 2003; Warr et al., 2005). The dose reduction is only required when dexamethasone used as antiemetics not as antitumor component of chemotherapy regimen. In setting of our study the medical team use 16 mg dose which was not

studied in clinical trials so the effect of dexamethasone in this dose is still questionable and require further studies.

Etoposide is a chemotherapeutic agent that is metabolized by CYP3A4; significant interaction with aprepitant is suspected (CYP3A4 inhibitors), but clinical trials failed to approve such clinically significant interaction and chemotherapy doses were not adjusted in phase III trials. However, caution is still urged when using any chemotherapeutic agent that is metabolized by CYP3A4 (Aapro and Walko, 2010). In setting of our study, there is no changes in the dose that has been noticed.

Although theoretically, inducers of CYP450 2C8 and/or 3A4 may decrease the plasma concentrations of paclitaxel, which is metabolized by these isoenzymes when given concomitantly, clinically no changes are recommended by clinical trials (Spencer and Faulds, 1994). Monitoring for the evidence of reduced therapeutic response to paclitaxel during coadministration with dexamethasone must be taken in consideration (http://www.abraxane.com/wpcontent/uploads/Abraxane_Prescribing_Information.pdf., Access date: 20/3/2016).

Caution and monitoring were urged when doxorubicin is coadministrated with CYP450 3A4 inducers such as dexamethasone; potentially a reduced efficacy of doxorubicin is suspected although it is not clinically applicable(Lee and Lee M, 1999). In our study, there is no changes in paclitaxel or doxorubicin doses that was been noticed.

Leucovorin and fluorouracil combination is used in the treatment of metastatic colon cancer, when 5-FU is coadministered with leucovorin, lower doses of 5–FU may be required and close monitoring for 5-FU toxicity such as neutropenia, thrombocytopenia, stomatitis, gastrointestinal hemorrhage, severe diarrhea, vomiting, cutaneous reactions and neuropathy are essential. The concomitant use of 5-FU with leucovorin increases both pharmacological and toxic effect of the former. Although in a study of elderly patient's receiving weekly leucovorin and 5-FU reported a higher incidence of death due to severe enterocolitis, diarrhea and dehydration, other studies concluded that 5-FU plus LV at a price of a higher toxicity is more active

than 5-FU alone without improving survival and progression-free survival (Nobile et al.,1992) .

We noticed the presence of diarrhea as a side effect in patients receiving combination of leucovorin and fluorouracil but we could not correlate it to drug interactions and there are no interventions were done specially for these patients.

If chronic dexamethasone therapy were given to the patients, the therapeutic and toxic effects of irinotecan is decreased by increasing irinotecan clearance via multiple mechanisms, therefore increase irinotecan dose may be required(serious interaction) (Friedman et al., 1999). If dexamethasone was used as antiemetic therapy, the effect on irinotecan metabolism and clearance is unknown and no clinical intervention seems to be necessary (Friedman et al., 1999). The patients who received dexamethasone in our study take dexamethasone as antiemetic therapy and no intervention is seemed to be necessary, however regular monitoring is required.

During the observation and follow up periods 6% of patient were completely not responded (failure) to antiemetic therapy which is given to control delayed nausea and vomiting after the first chemotherapy cycle. To understand the reasons behind this failure, the dose and duration of t antiemetic therapy as well as adherence of the patients were assessed.

Surprisingly, patients unresponded to antiemetic drugs therapy denied receiving any information about antiemetic treatment neither by the medical team nor from the pharmacist who dispense the medication. There was a case who admitted to the hospital after two days of the first chemotherapy cycle, the patient received high emetogenic chemotherapy and physician wrote suitable antiemetic drugs but unfortunately, according to the patient, no information was given to him related to the indication, dosing and necessity of drugs. Patient did not receive antiemetic medication for the following days and verbally expressed as “I didn’t know why or which time I will take this medication so I decided not to take medication until contacting with my physician after two weeks”. The significant differences in antiemetic response between educated and non-educated patients continue to the next two cycle where a complete control is never reached in patients not received

education during second and third cycle. From these observations we understand the importance of patient education to maintain complete control for CINV and this conclusion is not surprising and its approved by many studies. Educated patient can detect omitted premedication, wrong infusion intervals, leaking infusion and incorrect doses (Fernsler & Cannon, 1991; Schwappach and Wernli, 2010; Shah et al., 2006).

The patient must receive information related to acute therapy issues such as adverse effects and dosing regimen, administration issues for example drug taking with or without food, whether or not capsule can take apart or dissolved its content or tablet can or cannot be crushed, missing dose and extra dose. Patients may also need education on proper handling and storage of medication.

Patient education is a multidisciplinary process that requires collaboration between medical team to ensure the accessibility of sufficient .

Clinical pharmacists' involvement in patient education programs bridge the gaps between patients and physicians (Francis & Abraham, 2014; Sessions et al., 2010). Clinical pharmacist contributes to outcomes of pharmacotherapy by educating and counseling patients and motivate them to adhere to therapeutic regimen and monitoring plan (Yamada and Nabeshima, 2015). In some countries like United States, South Korea and Japan, the role of clinical pharmacist in patient education is expanded and pharmacist - managed clinic for cancer chemotherapy, palliative care, asthma, anticoagulation were emerged (Pauley et al., 1995; Reinders and Steinke, 1979; Morreale, 1995; Yamada and Nabeshima, 2015; Choe et al., 2002). In a cross–sectional survey, patients are intrigued with visiting a pharmacist during chemotherapy treatment and may be inclined to pay for a pharmacy counseling (McKee et al, 2011). The beneficial effect of oncology pharmacist were proved in a retrospective study by clinical and cost saving interventions and feedbacks from patients (Ruder et al., 2011). The effectiveness of oral chemotherapy management clinic which provides comprehensive medication therapy management services including education on various oral chemotherapy agents, concurrent medications and symptom management. An insurance assistance was assessed in a retrospective observational cohort which indicated that this clinic is effective in delivering early

interventions, resulting in decreased rates of adverse effects, nonadherence, drug interactions and medication errors over time (Wong et al., 2014).

The impact of implementation of a pharmacist-led oral chemotherapy-monitoring program was evaluated through cohort study where patients evaluated for number of interventions, adherence to laboratory parameter monitoring and overall time on each therapy and the author concluded that oral chemotherapy treatment outcomes can be maximized with the addition of a formalized monitoring program directed by an oncology pharmacist (Patel et al., 2015). Similar study showed a positive impact on chronic myelogenous leukemia (Lam and Cheung, 2015).

A study evaluated the outcome differences between pharmacist and physician driven management of CINV in adult hospitalized cancer patients and showed that there is no difference between the two groups in the primary outcome. However, there was a difference in adherence to the institution CINV guidelines (Elshaboury & Green, 2011). The effects of pharmaceutical care by reviewing the antiemetic protocol and giving recommendations to patients were analyzed through a 4-month longitudinal prospective intervention study. The study concluded that the pharmaceutical intervention by the pharmacists reduces the incidence of delayed CINV and improve medication adherence (Caracuel et al., 2014).

Our research is observational designed to describe real world in the hospital and investigate the reasons of inappropriate response to antiemetic drugs, without any interventions to change these realities which makes the internal validity of this research high. However, external validity which measures the degree to which the conclusion in our study would hold for other hospitals in other places in Turkey and at another time is low, as the research was done in a single center. Another drawback of our study is the patient's self reporting to incidence of nausea and vomiting, since it is a practical method for outpatient setting which leads to increased risk of subjectivity and recall bias.

This study aimed to assess the pharmaceutical care needs for oncology patients with CINV and highlighted factors that lead to inappropriate response to antiemetic therapy. Several questions arise from the study which could be addressed in future

studies. Based on these finding, recommendation for future studies is explained as the followings.

Pharmacoeconomic study is required to determine the impact of inappropriate response to antiemetic therapy on the total health cost, cost of extra antiemetic therapy, cost for the treatment of adverse effects of over or under prescription of antiemetics, cost of health care providers, etc. Interventional studies are required to determine the impact of clinical pharmacist interventions in improvement and management of CINV and optimize pharmaceutical care services. Cost effectiveness study of clinical pharmacist's interventions in the oncology patients direct care is another area to be studied. Studies to discuss the role of clinical oncology pharmacist in the patient counsling must have attention in the future studies.

As a conclusion, in this study a high percentage of non adherence with guidelines for prevention of CINV, especially in acute phase was noticed. A decrease in the efficacy and increase in side effects with these nonadherences was observed. High percentage of significant interaction was seen. Insufficient patient counseling which resulted in treatment failure was observed.

This study demonstrates that, the pharmaceutical care needs for the management of CINV in oncology patients includes ensuring adherence to international guidelines for antiemetic drugs, enhancing rational antiemetic use, appropriate antiemetic selection according to chemotherapy level of emetogenicity, appropriate dose, duration and frequency. Monitoring of side effects and optimization of palliative care are another area that must taken in consideration while developing any pharmaceutical care plan. The incidence of Drug – drug interactions are steadily increasing in oncology population and the probability of interactions increases with the number of drugs taken. These interactions can occur between chemotherapy and antiemetic or antiemetic therapy and chronic medications used to treat comorbidities and may lead to serious adverse effects or reduce the therapeutic effect of some compounds. A special care is required for identification of these interactions and determination of the necessary interventions as appropriate time for the administration of antiemetic drugs, avoid administration of other drug, etc.

Another area which requires special pharmaceutical care is patient education. The patients and families have the rights to be informed about diseases, drugs and its related issues. Patient education improves knowledge acquisition, enhanced self-care, reduced anxiety, enhanced self-concept and self-esteem, increased satisfaction with care, improved pain control, improved oral status, and reduced disruption in daily functioning.

Multidisciplinary team which includes clinical oncology pharmacists become an urgent need to ensure best services for these sensitive population. Studies proved a positive impact of clinical pharmacists in the management of cancer treatment and palliative care, they can introduce individualized treatment plans, monitoring chemotherapy together with nursing staff and providing patient education.

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9. ATTACHMENTS

Appendix 1

Marmara Üniversitesi Tıp Fakültesi
Klinik Araştırmalar Etik Kurulu

BAŞVURU BİLGİLERİ	PROTOKOL KODU	09.2014.0178	70737436-050.06.04-
	PROJE ADI	Kemoterapi kaynaklı bulantı-kusma tedavisi alan hastaların farmasötik bakım gereksinimlerinin saptanması	
	SORUMLU ARAŞTIRICI ÜNVANI/ADI	Doç.Dr. Mesut SANCAR	

KARAR BİLGİLERİ	Tarih 05.09.2014 Yukarıda başvuru bilgileri verilen araştırma başvuru dosyası ve ilgili belgeler araştırmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş ve gerçekleştirilmesinde sakınca bulunmadığı için Kurulumuzca onaylanmasına oy birliği ile karar verilmiştir. Onay sonrasında yapılacak her türlü proje değişiklikleri (tasarımcılar, başlık vb.) veya protokol değişikliklerinin Etik Kurula bildirilerek proje onayının yenilenmesi gerekmektedir.

ÜYELER

Unvanı / Adı / Soyadı	Uzmanlık Dalı	Kurumu / EK Üyeliği	Onaylanan Proje ile İlişkisi	Toplantıya katılım	İmza
Prof.Dr. Haner DİRESKENELİ	Romatoloji	M.Ü Tıp Fakültesi/ Başkan	Var Yok	Evet Hayır	
Prof.Dr. Tülin ERGUN	Dermatoloji	M.Ü Tıp Fakültesi/Başkan Yrd.	Var Yok	Evet Hayır	
Prof.Dr. Handan KAYA	Patoloji	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Prof.Dr. M.Bahadır GÜLLÜOĞLU	Genel Cerrahi	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Prof.Dr. Atila KARAALP	Farmakoloji	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Prof.Dr. Semra SARDAŞ	Eczacı	M.Ü Eczacılık Fak./Üye	Var Yok	Evet Hayır	
Prof.Dr. Başak DOĞAN	Diş Hekimi	M.Ü Diş Hekimliği Fak./Üye	Var Yok	Evet Hayır	
Doç.Dr. Elif AYDINER KARAKOÇ	Çocuk Sağlığı ve Hastalıkları Anabilim Dalı	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Doç.Dr. Besie Melek ATASOY	Radyasyon Onkolojisi	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Doç.Dr. Meltem KORAY	Diş Hekimi	İstanbul Üniv. Diş Hekimliği Fak./Üye	Var Yok	Evet Hayır	
Doç.Dr. Tolga GÜVEN	Tıp Tarihi ve Etik	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Doç. Dr. Gürkan SERT	Halkbilgisi	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Yrd.Doç.Dr. Figen DEMİR	Halk Sağlığı	Acıbadem Üniv. Tıp Fak.	Var Yok	Evet Hayır	
Yrd.Doç.Dr. Pınar Mega TİBER	Biyofizik	M.Ü Tıp Fakültesi/Üye	Var Yok	Evet Hayır	
Av.Ümit ERDEM	Sağlık Mensubu olmayan Kişi	Serbest	Var Yok	Evet Hayır	

Appendix 2

T.C.
SAĞLIK BAKANLIĞI
Türkiye İlaç ve Tıbbi Cihaz Kurumu

Giden Evrak Servisi
Giden Evrak No: 57474
Giden Evrak Tarihi: 14.05.2015
Güvenlik Kodu: 253078
İşlem Takip No: 1701162

Sayı : 26247029-514-05-01
Konu : Gözlemsel Çalışma [2015-PMS-14]

Sayın Doç. Dr. Faysal Dane
Marmara Üniversitesi Pendik Eğitim ve Araştırma Hastanesi
İç Hastalıkları Anabilim Dalı
Onkoloji Bilim Dalı

İlgi : Bakanlık evrak kayıt 06.05.2015 tarih, 0090700 sayılı ve 1701162 e-takip numaralı yazınız.

Doç. Dr. Faysal Dane sorumluluğunda yapılması planlanan ve aşağıda bilgileri verilen çalışma başvuru dosyası ilgili mevzuat gereğince incelenmiş olup;

Bakanlık evrak giriş 02.03.2015 tarih ve 0041700 sayılı yazı ekinde belirtilen merkezlerde çalışmanın başlaması uygun bulunmuştur.

Araştırmanın Adı :	Kemoterapi kaynaklı bulantı-kusma tedavisi alan hastaların farmasötik bakım gereksinimlerinin saptanması
Koordinatör Merkez:	Marmara Üniversitesi Pendik Eğitim ve Araştırma Hastanesi
Koordinatör /Sorumlu Araştırmacı:	Doç. Dr. Faysal Dane

Çalışmanın güncel Helsinki Bildirgesine ve Gözlemsel İlaç Çalışmaları Kılavuzuna uygun olarak yürütülmesi,

Çalışmaya, hakkında bilgi toplanan etkin maddeyi içeren tüm müstahzarların dahil edilmesi,

Standart tıbbi bakımın dışında gerekli olabilecek tüm işlemlerin destekleyici, destekleyici yoksa koordinatör hekim (tek merkezli çalışmalarda katılımcı hekim) tarafından karşılanması,

Hasta çalışmaya dahil edilmeden önce tedavisine başlanılmış olması,

Bu belge 5070 sayılı Elektronik İmza Kanunu uyarınca elektronik olarak imzalanmıştır.
Doküman https://e-islemler.titck.gov.tr/eimza/eimzakontrol.aspx adresinden kontrol edilebilir.
Güvenli elektronik imzalı aslı ile aynıdır.

Sögütözü Mahallesi,2176.Sokak No:5 06520 Çankaya/ANKARA
Tel: (0 312) 218 30 00– Fax : (0 312) 218 33 54
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Appendix 3

GÖNÜLLÜ ONAY FORMU

Yukarıda gönüllüye araştırmadan önce verilmesi gereken bilgileri gösteren metni okudum. Bunlar hakkında bana yazılı ve sözlü açıklamalar yapıldı. Bu koşullarla söz konusu klinik araştırmaya kendi rızamla hiçbir baskı ve zorlama olmaksızın katılmayı kabul ediyorum.

Gönüllünün Adı-soyadı: İmza Adress

Tel :

Araştırmacı Adı –Soyadı: imza adress

Tel:

Tanıklık eden kuruluş görevlisinin:

Adı – soyadı: imza adress:

Tel:

Appendix 4

HASTA PROFİL KAYDI

Doğum Tarihiniz:.....

Şehir:..... **İlçe (semt):**.....

Medeni Haliniz: Bekar □ Evli □ Diğer □

Cinsiyetiniz: KADIN □ ERKEK □

Eğitim Durumunuz:

İlköğretim □

Ortaokul □

Lise □

Üniversite □

Yüksek lisans, doktora, v.b. □

Hiçbiri □

Sigara içiyor musunuz?

EVET □ HAYIR □

Alkol kullanıyor musunuz?

EVET □ HAYIR □

Aşağıdaki kronik hastalıklardan hangisi sizde mevcuttur?

Astım □	Konjestif Kalp Yetmezliği □	Reflü □ Gastrit □
Hipertansiyon □	Kronik Obstrüktif Akciğer Hastalığı □	Kronik duedonum ülseri □
Osteoporoz □	Hiperlipidemi □	Diyabet Tip1/ Tip2□
Hipotiroidi □	Hipertiroidi □	Diğer □

Hastalığın tanı nedir?

Düzenli olarak kullandığınız ilaçlar ve gıda takviyeleri nelerdir?

Geçirdiğiniz operasyonlar veya gerçekleşmesi planlanan operasyonlar nelerdir?

Appendix 5

GÜNLÜK HASTA İZLEM KARTI bulantı şiddet:

Tarih:

1 2 3 4 5 6 7

Hasta adı :

hiç şiddetli

Kusma saysı:

	kusma	Bulantı şiddet
Gün 1		
Gün2		
Gün 3		
Gün 4		
Gün 5		

Eğer kusma devam ederseniz
İlave tedavi:

Var	Yok .
İlaç adı:	İlaç saysı:
Gün 1	
Gün2	
Gün3	
Gün4	
Gün5	

Kusma sebapeyle hastaneye yatış :

var	Yok	Kaç gün	Hangi hastane

Appendix 6

Fonksiyonel Yaşam Ölçeği -Kanser

Lütfen aşağıdaki sorulara **son iki hafta içindeki** aktivitelerinize ve sağlık durumunuza göre cevap veriniz.

1. Çoğu insan zaman zaman depresyon belirtileri hisseder. Siz bu duyguları ne kadar sıklıkla hissediyorsunuz?

1 2 3 4 5 6 7

Hiçbir zaman Sürekl

2. Günlük yaşamınızdaki sorunlarınızı kolay çözebiliyor musunuz?

1 2 3 4 5 6 7

İyi değil Çok iyi

3. Hastalığınız ne kadar sık aklınıza geliyor?

1 2 3 4 5 6 7

Devamlı Hiçbir zaman

4. Dinlenmeye fırsat bulabiliyor musunuz?

1 2 3 4 5 6 7

Fırsat bulabiliyorum Hiç fırsat bulamıyorum

5. Bulantı günlük işlerinizi etkiliyor mu?

1 2 3 4 5 6 7

Hiç etkilemiyor Çok etkiliyor

6. Bugün kendinizi ne kadar iyi hissediyorsunuz?

1 2 3 4 5 6 7

Son derece kötü Son derece iyi

7. Bugün kendinizi yemek pişirecek / küçük ev işleri yapabilecek kadar yeterli hissediyor musunuz ?

1 2 3 4 5 6 7

Çok yeterli Çok yetersi

Lütfen aşağıdaki sorulara **son iki hafta içindeki** aktivitelerinize ve sağlık durumunuza göre cevap veriniz.

8. Son iki haftada hastalığınız yakınlarınıza zorluk yaşattı mı?

1 2 3 4 5 6 7
Hiç zorluk yaşatmadı — Çok fazla zorluk yaşattı

9. Yaşama isteğinizin azaldığını ne sıklıkla hissediyorsunuz?

1 2 3 4 5 6 7
Daima — Hiçbir zaman

10. Son bir ay içinde iş yerinde / evdeki verimliliğinizden memnun musunuz?

1 2 3 4 5 6 7
Hiç memnun değilim — Çok memnunum

11. Bugün kendinizi ne kadar huzursuz hissediyorsunuz?

1 2 3 4 5 6 7
Hiç huzursuz hissetmiyorum — Çok huzursuz hissediyorum

12. Size göre. hastalığınız. son iki haftada. en yakınlarınızla ilişkilerinizi ne kadar bozdu?

1 2 3 4 5 6 7
Tamamen bozdu — Hiç bozmadı

13. Ağrı ya da rahatsızlıklar günlük aktivitelerinizi ne kadar etkiliyor?

1 2 3 4 5 6 7
Hiç etkilemiyor — Çok etkiliyor

14. Son iki haftada hastalığınız size kişisel olarak ne kadar zorluk yaşattı?

1 2 3 4 5 6 7
Çok fazla zorluk yaşattı — Hiç zorluk yaşatmadı

Lütfen aşağıdaki sorulara **son iki hafta içindeki** aktivitelerinize ve sağlık durumunuza göre cevap veriniz.

15. Ev ile ilgili günlük sorumluluklarınızın ne kadarını tamamlayabiliyorsunuz?

1 2 3 4 5 6 7
Hepsini Hiçbirini

16. Son iki haftada en yakınlarınızı görmeye / onlarla birlikte zaman geçirmeye ne kadar istekliydiniz?

1 2 3 4 5 6 7
İsteksizdim Çok istekliydi

17. Son iki haftada kaç kez bulantınız oldu?

1 2 3 4 5 6 7
Hiç olmadı Çok fazla oldu

18. Gelecekten ne kadar korkuyorsunuz?

1 2 3 4 5 6 7
Devamlı korkuyorum Hiç korkmuyorum

19. Son iki haftada arkadaşlarınızı görmeye / onlarla birlikte zaman geçirmeye ne kadar istekliydiniz?

1 2 3 4 5 6 7
İsteksizdim Çok istekliydim

20. Sizce son iki haftada yaşadığınız ağrı ya da rahatsızlıkların ne kadarı hastalığınızla ilgiliydi?

1 2 3 4 5 6 7
Hiçbiri Hepsi

21. Size uygulanan tıbbi tedaviye ne kadar güveniyorsunuz?

1 2 3 4 5 6 7
Hiç güvenmiyorum Çok güveniyorum

22. Sizce bugün nekadar iyi görünüyorsunuz?

1 2 3 4 5 6 7
Son derece kötü Son derece iyi

Fonksiyonel Yaşam Ölçeği'nin Alt Başlıkları

Alt başlıklar	Soru numarası
Fiziksel Fonksiyonlar	4.6.7.10.11.13.15.20.22
Psikolojik Fonksiyonlar	1.2.3.9.18.21
Genel İyilik Hali (Kanserle İlgili Güçlükler)	8.12.14
Sosyal Fonksiyonlar	16.19
Gastrointestinal Semptomlar (Bulantı)	5.17

Ölçek 7'li Likert Ölçeği'ne göre hazırlanmıştır ve ölçekte seçenekler olumludan olumsuza doğru sıralanan yedi katogoriden oluşmaktadır. Fonksiyonel Yaşam Ölçeği'ndeki seçenekler olumsuz sorular için 7.6.5.4.3.2.1; olumlu sorular için 1.2.3.4.5.6.7 olarak puanlandırılmıştır. 2. 3. 6. 9. 10. 12. 14. 16. 18. 19. 21. 22 nolu sorular sütunun sağına doğru olumlu. geri kalan 1. 4. 5. 7. 8. 11. 13. 15. 17. 20 nolu sorular sütunun sağına doğru olumsuz olarak değerlendirilmiştir. Ölçek sonuçları her bir sorunun puan değeri toplanarak bulunmuştur. Ölçekte maksimum puan 154. minumum puan 22'dir ve yüksek puanlar fonksiyonel durumun ve yaşam kalitesinin çok iyi olduğunu göstermektedir.

Schipper H. Clinch J. McMurray A. et all. (1984). Measuring the quality of life of cancer patients: The functional living index-cancer: Development and validation. J Clin Oncol; 2 (5):472-483.

Bektaş HA. Akdemir N. (2008) "Reliability and Validity of the Functional Living Index – Cancer (FLIC) in Turkish Cancer Patients". Cancer Nursing: An International Journal for Cancer Care; 31 (1): E1-E7. (SSCI)

Bektaş HA. Akdemir N. (2006) "Kanserli Bireylerin Fonksiyonel Durumlarının Değerlendirilmesi." Türkiye Klinikleri Tıp Bilimleri Dergisi; 6(5): 488-499.

Appendix 7

Fonksiyonel Yaşam Ölçeği –Emezis

Bulantı Bölümü

1. Bulantı sayısı

1 2 3 4 5 6 7

2. Gündelik aktivitelerini veya boş vakitlerindeki genel faaliyetleri sürdürebilme becerisi

1 2 3 4 5 6 7
Hiç Normal

3. Yemek hazırlama veya ufak çaplı ev işleri yapma becerisi

1 2 3 4 5 6 7
Hiç Normal

4. Yemekten zevk alabilme

1 2 3 4 5 6 7
Hiç Normal

5. Serinletici içeceklerden zevk alabilme

1 2 3 4 5 6 7
Hiç Normal

6. Aile ve arkadaşlarla vakit geçirme isteği

1 2 3 4 5 6 7
Hiç isteksizdim Çok istekliyidim

7. Günlük işlevlerden etkilenme

1 2 3 4 5 6 7
çok Hiç

2. kişisel zorluklara maruz kalma

1 2 3 4 5 6 7
çok Hiç

9. diğer zorluklara maruz kalma

1 2 3 4 5 6 7
çok Hiç

Kusma Bölümü

10. kusma sayısı

1 2 3 4 5 6 7

11. Gündelik aktivitelerini veya boş vakitlerindeki genel faaliyetleri sürdürebilme becerisi

1 2 3 4 5 6 7
Hiç Normal

12. Yemek hazırlama veya ufak çaplı ev işleri yapma becerisi

1 2 3 4 5 6 7
Hiç Normal

13. Yemekten zevk alabilme

1 2 3 4 5 6 7
Hiç Normal

14. Serinletici içeceklerden zevk alabilme

1 2 3 4 5 6 7
Hiç Normal

15. Aile ve arkadaşlarla vakit geçirme isteği

1 2 3 4 5 6 7
Hiç isteksizdim Çok istekliyidim
isteksizdim

16. Günlük işlevlerden etkilenme

1 2 3 4 5 6 7
çok Hiç

17. Kişisel zorluklara maruz kalma

1 2 3 4 5 6 7
çok Hiç

18. Diğer zorluklara maruz kalma

1 2 3 4 5 6 7
çok Hiç

Appendix 8

Yan Etki Anketi

Lütfen aşağıdaki soruları cevaplayın

Aşağıdaki Rahatsızlıklardan Sahip misiniz?

Semptomlar	Hayır	Evet Hafif	Orta	Şiddetli
Eklam ağrısı	☐	☐	☐	☐
Sırıt ağrısı	☐	☐	☐	☐
Kas ağrısı	☐	☐	☐	☐
Genel halsizlik	☐	☐	☐	☐
Karın ağrısı	☐	☐	☐	☐
Kabızlık	☐	☐	☐	☐
İshal	☐	☐	☐	☐
Baş ağrısı	☐	☐	☐	☐
Flatulence	☐	☐	☐	☐
Mide bulantısı	☐	☐	☐	☐
Yutma problemi	☐	☐	☐	☐
Kusma	☐	☐	☐	☐
Hazımsızlık	☐	☐	☐	☐
Koyu Renkli Dışkılama	☐	☐	☐	☐
Diş Eti Kanaması	☐	☐	☐	☐
Sık İdrara Çıkma	☐	☐	☐	☐
İdrarda Kan Görme	☐	☐	☐	☐
İdrar Yaparken Yanma	☐	☐	☐	☐

Koyu Renkli İdrar	☐	☐	☐	☐
İdrar Miktarında Azalma	☐	☐	☐	☐
Yorgunluk	☐	☐	☐	☐
Baş Ağrısı	☐	☐	☐	☐
Uyku Hali	☐	☐	☐	☐
uyuşukluk	☐	☐	☐	☐
Hafıza kaybı	☐	☐	☐	☐
Denge kaybı	☐	☐	☐	☐
İştah kaybı	☐	☐	☐	☐
Titreme	☐	☐	☐	☐
Susuzluk	☐	☐	☐	☐
Depresyon	☐	☐	☐	☐
Işığı Hassasiyet	☐	☐	☐	☐
Stress	☐	☐	☐	☐
Karışıklık	☐	☐	☐	☐
Konsantrasyon kaybı	☐	☐	☐	☐
Güvenlik açığı	☐	☐	☐	☐
Nefes alma zorluğu	☐	☐	☐	☐
Öksürük	☐	☐	☐	☐
Boğaz ağrısı	☐	☐	☐	☐
Grip	☐	☐	☐	☐
Hapşurma	☐	☐	☐	☐
Burun kanaması	☐	☐	☐	☐
Kaşıntı	☐	☐	☐	☐

Cilt kuruluğu	☐	☐	☐	☐
Şişkinlik	☐	☐	☐	☐
Cilt kuruluğu	☐	☐	☐	☐
Aşırı terleme	☐	☐	☐	☐
Ciltte kırmızı döküntü	☐	☐	☐	☐
Göz ağrısı	☐	☐	☐	☐
Görme bozukluğu	☐	☐	☐	☐
Çarpıntı	☐	☐	☐	☐
Ateş	☐	☐	☐	☐
Kulaklarda çınlama	☐	☐	☐	☐
Flushing	☐	☐	☐	☐
Solgunluk	☐	☐	☐	☐

Teşkkur Ederiz

Appendix 9

MASCC Guidelines 2014

SUMMARY ACUTE NAUSEA AND VOMITING

EMETIC RISK GROUP	ANTIEMETICS
High	$5HT_3$ + DEX + APR or FOS
Anthracycline + Cyclophosphamide (AC)	$5HT_3$ + DEX + APR or FOS
Moderate (other than AC)	PALO + DEX
Low	DEX OR $5HT_3$ OR DRA
Minimal	No routine prophylaxis

$5HT_3$ = serotonin receptor antagonist	DEX = DEXAMETHASONE	APR = APREPITANT; FOS= FOSAPREPITANT	PALO = PALONOSETRON	DRA = dopamine receptor antagonist

*** NOTE: If the NK1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.**

The Antiemetic Subcommittee of The Multinational Association of Supportive Care in Cancer. - Ann Oncol 2010; www.mascc.org.

Multinational Association of Supportive Care in Cancer

Supportive Care Makes Excellent Cancer Care Possible

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SUMMARY DELAYED NAUSEA AND VOMITING

EMETIC RISK GROUP	ANTIEMETICS
High	DEX* + APR*
Anthracycline + Cyclophosphamide (AC)	APR or none**
Moderate (other than AC)	DEX
Low	No routine prophylaxis
Minimal	No routine prophylaxis

DEX = DEXAMETHASONE	APR= APREPITANT

*** DEX only, if FOSAPREPITANT used on Day 1**

**** If FOSAPREPITANT used on Day 1**

The Antiemetic Subcommittee of The Multinational Association of Supportive Care in Cancer. Ann Oncol 2010; www.mascc.org

Multinational Association of Supportive Care in Cancer

Supportive Care Makes Excellent Cancer Care Possible

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10. CURRICULUM VITAE

Name	Nibal	Surname	Abunahlah
Birth Place	Gaza	Birth Date	23.12.1980
Nationality	Palestinian	E-mail	nibal.abunuhlah@kemerburgaz.edu.tr nebal_hasan@yahoo.com

Education

	Name of Graduation Foundation	Graduation Year
PhD Education	Marmara University Clinical Pharmacy Department	2012 -
Master Degree	Alexandria University Clinical Pharmacy Department	2008
University	Alazhar University Faculty of Pharmacy	2002
High school	Khan Younis - Girls -A Secondary School	1997

Working Experience

Job	Company	Duration(Year-Year)
Pharmacist	Private pharmacy	2002-2004
Clinical pharmacist	Nasser Medical Center	2004-2011
Clinical Pharmacy Lecturer	Istanbul Kemerburgaz University	2014- Until Now

Foreign Languages	**Reading***	**Speaking***	**Writing***
English	Very Good	Very Good	Very Good
Arabic	Very Good	Very Good	Very Good
Turkish	Very Good	Very Good	Very Good

Foreign Language Exam Evaluation*

YDS	**UDS**	**ILETS**	**TOFEL IBT**	**TOFEL PBT**	**FCE**	**CAE**	**CPE**
			84				

Computer Knowledge

Program	**Usage Skill**
Microsoft Office	Very Good

*Please estimate very good. good. medium. weak.

Conferences and Presentations

Date	**Activity**
1/4/2016	Nibal Abunahlah . Abdullah Olgun . Akgül Yeşilada "Integrating a new assessment strategy to improve didactic outcome and self-learning in pharmacotherapy courses in Istanbul Kemerburgaz University". The Online Journal of Quality in Higher Education - April 2016 Volume 3, Issue 2
2- 4/12/2015	`Nibal Abunahlah . Abdullah Olgun . Akgül Yeşilada "Integrating a new assessment strategy to improve didactic outcome and self-learning in pharmacotherapy courses in Istanbul Kemerburgaz University" (poster) ICQH 2015. International Conference on Quality in Higher Education Sakarya University. Turkey.
27-29/12/2015	Nibal Abunahlah. Mesut Sancar.Fikret.V.İzzettin. Faysal Dane. Mustafa Kerem Özyavuz "Determination of Potentially Drug-Drug Interaction in Oncology Patients(poster) IVEK Uluslararası İlaç ve Eczacilik Kongresi. Istanbul. Turkey http://ivekkongre.com/
28-30/10 2015	Nibal Abunahlah. Mesut Sancar.Fikret.V.İzzettin. Faysal Dane. Mustafa Kerem Özyavuz "Determination of Potential Drug-Drug Interaction in Oncology Patients" (poster) 44th ESCP. European Society of Clinical Pharmacy Symposium . Lisbon. Portugal
28-30/10 2015	Emine Karataş Koceberber. Nibal Abunahlah. Barkın Berk "Clopidogrel – Proton Pump Inhibitors Prescribing Habits in Turkey" (poster) 44th ESCP. European Society of Clinical Pharmacy Symposium . Lisbon. Portugal
29/9-3/10/ 2015	Nibal Abunahlah . Joseph Saseen . Kari Franson . Akgül Yeşilada " Inclusion of Interactive Clinical Case Studies to promote patient-centered care in a Pharmacotherapy Course in Istanbul Kemerburgaz University" (poster) FIP World Congress 2015. Düsseldorf. Germany
9-12/6/2015	Nibal Abunahlah. Jennifer Trujillo . Akgül Yeşilada "Incorporating Active Learning Strategies in Pharmacotherapy course in Istanbul kemerburgaz University(poster) International Symposium On

	Pharmaceutical Sciences". ISOPS 2015.Ankara. Turkey
22-24/10/2015	Nibal Abunahlah. Aygül Koseoğlu "Reuse and Reimbursement of the Surplus Chemotherapy in Turkish Hospital" (poster) 43rd ESCP Symposium On Clinical Pharmacy. Copenhagen. Denmark
14-15/2015	Nanobiotechnology Conference. Istanbul Kemerburgaz University (organization Committee). Istanbul . Turkey
28/11- 1/12/2013	Nibal Abunahlah. Mesut Sancar. Amro Elastal "Some Epidemiological Features of Chronic Obstructive Airway Disease" (poster) National Conference for Clinical Pharmacy and Pharmaceutical care . Antalya. Turkey
1-3/7/2011	Nibal Abunahlah "Pattern of Antibiotic Usage at Nasser Hospital". (Oral Presentation) Internal Medicine Conference. Gaza. Palestine