Assessment of Potential Drug-Drug Interactions in Hospitalized Cancer Patients

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Declaration

I certify that this research work titled "*Assessment of Potential Drug-Drug Interactions in Hospitalized Cancer Patients"* is my own work. The work has not been presented elsewhere for assessment. The material used from other sources has been properly acknowledged / referred.

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Copyright Statement

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Dedicated to my mother.

Abstract

Drug-Drug interactions are the altered pharmacological effects of drugs due to their interactions with another drug. Cancer patients are more prone to these types of interactions since concomitant use of multiple therapeutic ingredients is a common practice for managing the disease. The outcomes of these interactions can be detrimental as far as the quality of care is concerned. These events can not only prolong the stay of patient at the hospital but also have economic implications since the cancer treatment is very expensive. A failure to achieve the optimal therapeutic response and at times progression of disease state due to a possible delayed response of the drugs are examples of possible consequences of serious drug-drug interactions. A study was conducted at a tertiary care health setup to detect, report and identify potential drug-drug interactions in hospitalized cancer patients. All the prescribed/ administered pharmaceuticals were recorded and checked using credible drug references. Majority of the cases involved dexamethasone as one of the interacting drugs. Among the totally observed cases of drug interactions with dexamethasone more than 80% have shown that it minimizes the effect of the interacting co-administered pharmaceutical. Future studies should continue to investigate the mechanism of action in order to explore the prescription intervention avoiding such interaction.

Key Words: *drug- drug interactions, cancer chemotherapy, inpatient oncology department, prescription interventions*

Table of Contents

List of Figures

List of Tables

CHAPTER 1: INTRODUCTION

1. INTRODUCTION

1.1: Definition

Cancer refers to an uncontrolled growth and proliferation of cells that can affect almost any part of the body. The growth can metastasize to distant sites by invading surrounding tissues. A number of therapies are available now a days for treating various types of cancer(Organization, 2018).

1.2: Signs & Symptoms

- Development of new swelling or lump
- Unusual flow of blood
- A long-term cough
- Progressive weight loss
- Deviation in bowel actions

There are various disease which may show similar sign and symptoms, so it is very important to differentially diagnose before initiating cancer therapy(Juul et al., 2018).

1.3: Pathophysiology

There are various factors which are involved in cancer progression most of which are associated with use of tobacco containing agents. Alcohol use also lead towards cancer development which is reported in a number of studies(Rahman, Suresh, & Waly, 2018). Radiations are also cancer-causing agents. Excessive exposure to radiation by an individual may cause cancer(Patel et al., 2018). Pathophysiology of a disease plays a very important role in diagnosis since tissue biopsy is very helpful diagnostic technique in order to diagnose a particular type of cancer(Nair, Ramachandran, Joghee, Antony, & Ramalingam, 2018).

1.3.1: Prevention & Treatment

In the modern era there are a number of therapies available to treat various types of cancer(Ahles & Root, 2018). Some natural treatments are also available to control cancer including use of fruits, vegetables, nuts and cereals in natural condition without processing are very much

helpful(Jabir, Firoz, Bhushan, Tabrez, & Kamal, 2018). Smoking cessation is also very important to control cancer(Douglas, Henson, Drope, & Wender, 2018). Pharmaceutical care is very important to manage secondary infections(Robertson, 2018). Pharmacist in this way can play an important role to manage cancer in early stages by intervening and ensuring proper dosage regimen(Goodin, 2018).

1.4: Prevalence of Cancer

In 2012, 1479350 cases of cancer were documented, and more than 5 lac people breathe their last due to this deadly disease. Cancer is the second most extensive cause of death in United State of America. More than 40% of people born today will have cancer detection at some point in their life span. Analysis of data collected in 2012 tell us that 14.1 million new incidences of cancer occurred worldwide(Olshansky et al., 2005). Lung cancer, colorectal cancer, prostate cancer & stomach cancer are the most prevalent types of cancer in males, while breast cancer, colorectal cancer, lungs cancer & cervical cancer is the most common in females. Mostly cancer occur in developed countries and its risk increases with the increase in age. In 2012 approximately 1.65 lac children were diagnosed with different tumors with an exception in Africa where Non Hodgkin Lymphoma occurred more often(R. Lee & Fredrick, 2015; Siegel, Miller, & Jemal, 2015).

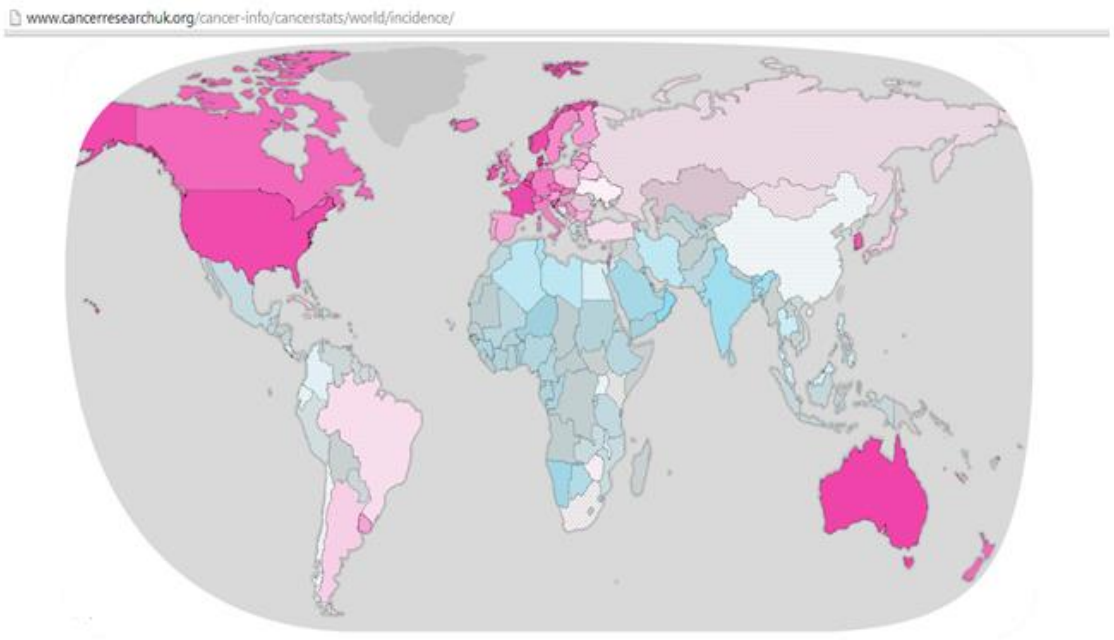


Figure 1.1: Worldwide Prevalence of Cancer

Table 1.1: Prevalence of Cancer in United States

Estimated 10 most common cancer cases in the United States in males and females (all races).				
Rank	**Males (766,130 Total Cases)**	**Percent**	**Females (713,220 Total Cases)**	**Percent**
1	Prostate	25	Breast	27
2	Lung and bronchus	15	Lung and bronchus	14
3	Colon and rectum	10	Colon and rectum	10
4	Urinary	7	Uterine corpus	6
5	Lymphoma	5	Lymphoma	5
6	Melanoma	5	Melanoma	4
7	Kidney and renal pelvis	5	Thyroid	4
8	Leukemia	3	Kidney and renal pelvis	3
9	Oral cavity	3	Ovary	3
10	Pancreas	3	Pancreas	3
	Other sites	19	Other sites	21

1.4.1: Prevalence of cancer in Pakistan:

Pakistan is having high rate of disease and is ranked seventh globally. Due to unstable political situation & socioeconomic concerns and being one of the most crowded country, cancer patients are not having access to the proper treatment according to modern techniques(Uqaili et al., 2018). According to cancer registry database system (KCR) held in Karachi prevalence of cancer is 51.8% in females whereas 48.1% in males. Among these 32.6% males have head & neck cancer and 38.2% females are suffering from breast cancer. Pakmedinet contains 175 papers related to cancer with only seven associated to cancer registration in Pakistan(Idrees, Fatima, Abdul-Ghafar, Raheem, & Ahmad, 2018; Rafiq & Jeppesen, 2018).

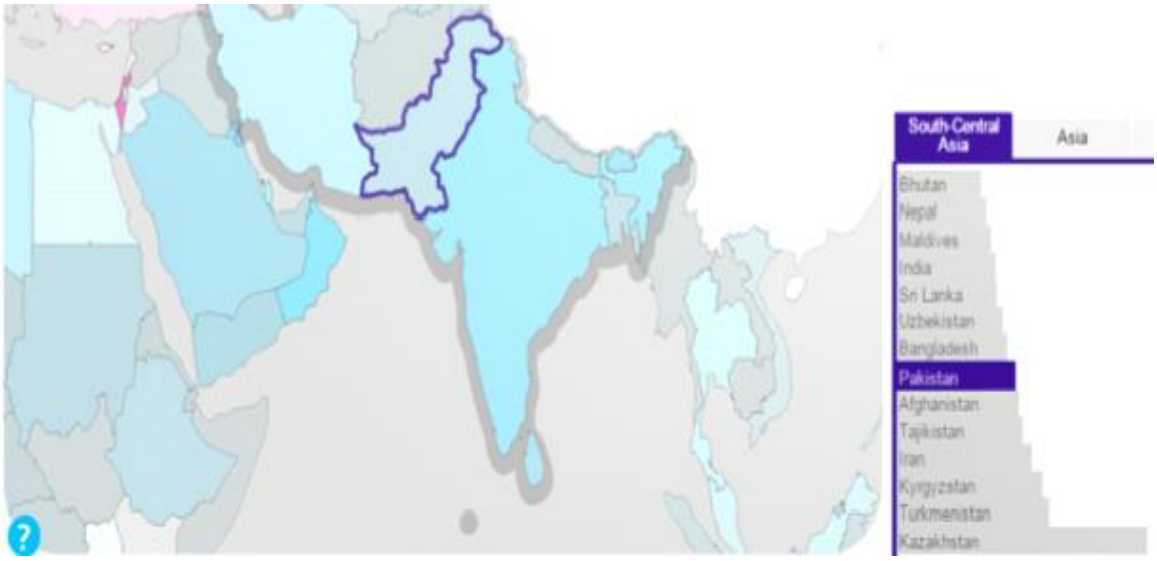


Figure 1.2: Prevalence of Cancer in Pakistan

It is estimated that only in Islamabad about 3000 cancer patients have access to cancer hospitals. The number of documented cancer cases is rising day by day. Due to existence of many alternative ways of treatment including various mythologies and socioeconomic reasons patients are sometimes reluctant to get treatment from hospitals(Khwankong, Sriplung, & Kerdpon, 2018).

Representation of Routine Medical Consultations:

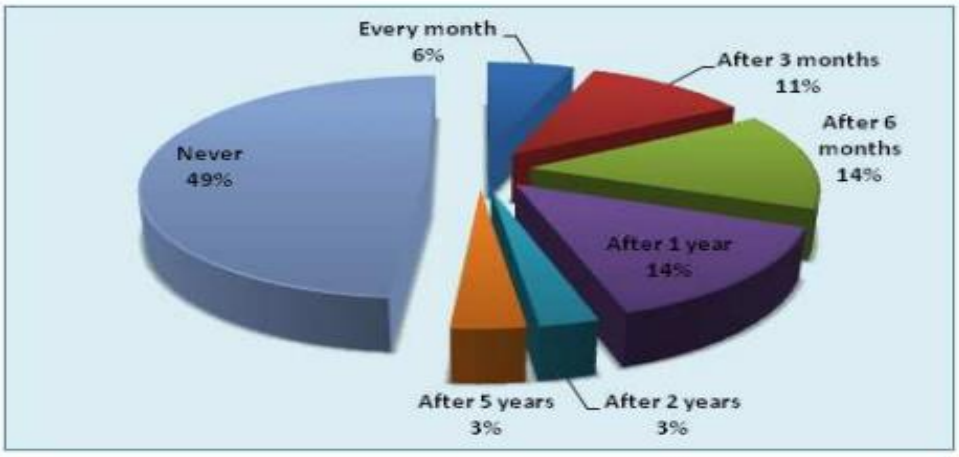


Figure 1.3: Representation of Routine Medical Consultations

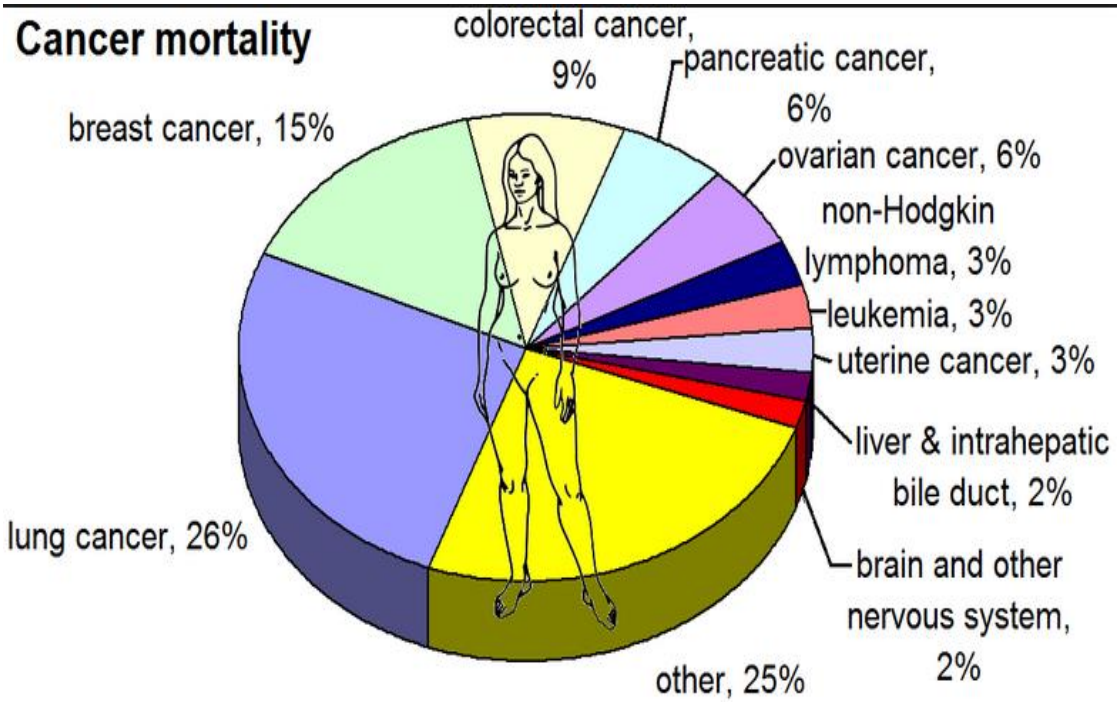


Figure 1.4: Mortality rate of cancer

1.5: Diagnostic Tools:

Diagnostics tools which are used for screening of cancers are as follows:

1. SPECT (Single-Photon Emission Computed Tomography)
2. PET (Positron-Emission Tomography)
3. CT Scan (Computed Tomography Scan)
4. MRI (Magnetic Resonance Imaging)
5. Biopsy
6. Biochemical tests
7. DEXA (Dual Energy X-Ray Absorptiometry)
8. Mammography

1.5.1: SPECT (Single-Photon Emission Computed Tomography):

It is a tomographic imaging method in nuclear medicine utilizing gamma beams. Gamma-emitting radioisotope is administered to the patient mainly in bloodstream through injection. A pointer radioisotope is linked to a specific ligand to make a radio ligands where the blend is seen by gamma cameras(Castellucci, Nanni, & Ambrosini, 2018; Werner et al., 2018).

1.5.2: PET (Positron-Emission Tomography):

Positron emission tomography is a hallmark radiological imaging technique to obtain 3-D medical images of various processes happening in the body(Cao, Bernard, Heutte, & Sabourin, 2018). This system has the capability to detect stream light of gamma beams radiated indirectly by a positron discharging radionuclide (tracer), which is introduced into the body through a chemically active moiety. The associated computer aided software develops the three dimensional images of tracer inclusion inside the body (Kishino et al., 2018; Shao et al., 2018; Van Son et al., 2018).

1.5.3: DEXA (Dual Energy X-Ray Absorptiometry):

This is a very efficient technique used for measuring bone mineral density (BMD) in order to access risk of osteoporosis and fracture.(Janiszewska, Raczkowski, Walczak, Składowski, & Maciejczyk, 2018; Mishra, Mohan, Chakravarty, & Poddar, 2019). Patient's bones are exposed to dual x-ray beams which transform to energy levels that can be evaluated from the absorption by the bone. The BMD is calculated by subtracting the amount of energy absorbed by the soft tissue using dimensional technique (Kumar, 2018; Li, Sun, Zhao, & Cai, 2019; Selvanambi et al., 2018).DEXA is classically helpful for the identification of osteoporosis. It can estimate the levels of osteoporosis. This technique is more helpful as compared to nuclear bone scan, because nuclear bone is susceptible for certain diseases of bones(Balasubramanian et al., 2018; Chandran, 2018).

1.1.5.4: CT-Scan (Computed-Tomography Scan):

CT-scan is a technique that uses computational method by utilizing x-rays to deliver tomographic descriptions (virtual 'slices') of specific regions of a scanned article, enabling to see inside without cutting(Ashvitha, ShilpaAarthi, Thamizhkkanal, Rajendiran, & Malathi, 2018;

Rani, 2018). Computerized geometry handling is utilized to create a three-dimensional image of within a body structure in a huge sequence of two-dimensional radiological images taken in the region of single axis rotation. Medical imaging is one of the most acceptable use of x- ray CT(Kaarthik & Vivek, 2018; S. Lee et al., 2018). Its cross-sectional images are utilized for diagnostic and therapeutic purposes in different medical areas.(Babu & Vijayalakshmi, 2019; Lun & Li, 2018).

1.5.5: Magnetic Resonance Imaging:

MRI (Magnetic Resonance Imaging), NMRT (Nuclear Magnetic Resonance Imaging) and MRT (Magnetic Resonance Tomography) is a medical imaging system utilized in radiology to look at the internal structures and physiology of the body for diagnostic and therapeutic purposes(Hamoen et al., 2018; Pizzi et al., 2018). Magnetic fields and radio waves are used to elucidate intricate descriptions of the body structures. The technique is widely used in hospitals setups for clinical investigations and diagnosis and for follow-up without exposure to ionizing radiation.(Hesketh & Brindle, 2018; Kuhl, 2019).

1.5.6: Mammography:

Mammography is the technique of utilizing low energy X-rays (more often around 30kVp) to study human breast tissues. It is utilized as a diagnostic and screening tool (Blanks et al., 2018; Yaffe et al., 2018). The objective of mammography is the before time detection of breast malignancy, traditionally through detection of feature masses and/or micro calcifications.

Like all X-rays, mammograms use dosages of ionizing radiation to create medical images. Radiologists then analyze the image for any abnormality. Usually lower energy X-rays than those utilized for radiography of bones is used in mammography. Ultrasound, positron (PEM), and magnetic resonance imaging (MRI) are closely related to mammography(Guo, Lu, Qin, & Fei, 2018; Kim et al., 2019). Ultrasound is typically utilized for further assessment of masses found on mammography or palpable masses not seen on the mammograms. If the mammogram is inconclusive ductograms is used for assessment (Melsaether, Raad, Helbich, Moy, & Pinker, 2018). MRI can be useful for additional evaluation of questionable conclusion as well as for screening pre-surgical evaluation in patients with known breast cancer to perceive any further lesions (Sulieman et al., 2018).

1.6: Biochemical Tests:

Different type of biochemical tests are advised such as:

- LFTs (liver function tests)
- CBC (complete blood Count)
- Urine Test (RE)
- Serum Creatinine Level
- Blood Urea
- Blood Glucose Level(Ma et al., 2018; Shiradkar et al., 2018; Zhang et al., 2018)

1.7: Treatment of Cancer

Table 1.2: Treatment choices for Cancer (Burkheimer et al., 2018)

Treatment choices for cancers responsive to systemic agents.

Diagnosis	Current Treatment of Choice	Other Treatments
Acute lymphoblastic leukemia (ALL)	**Induction combination chemotherapy:** Vincristine, prednisone, daunorubicin, asparaginase, intrathecal methotrexate	Imatinib mesylate (Ph positive ALL), autologous or allogeneic transplantation for high risk or at relapse
	Consolidation combination chemotherapy: Cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD) alternated with cytarabine, methotrexate	
	Maintenance chemotherapy: Methotrexate, 6-mercaptopurine	
Acute myeloid leukemia (AML)	**Combination chemotherapy:** Cytarabine, daunorubin or Cytarabineidarubicin	Gemtuzumab ozogamicin, prednisone, doxorubicin
Chronic myeloid leukemia (CML)	Imatinib mesylate	Dasatinib, nilotinib, allogeneic bone marrow transplantation, hydroxyurea, interferon-α, cytarabine, busulfan
Chronic lymphocytic leukemia (CLL)	**Combination chemotherapy:** Fludarabine, cyclophosphamide, rituximab (FCR); or Fludarabine, or Chlorambucil	Alemtuzumab, bendamustine, pentostatin, cladribine, cyclophosphamide, vincristine, doxorubicin, prednisone
Hairy cell leukemia	Cladribine (2-chlorodeoxyadenosine)	Pentostatin, interferon-α
Hodgkin disease (stages III and IV)	**Combination chemotherapy:** Doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) or Doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone (Stanford V)	Gemcitabine, vinorelbine, ifosfamide, cyclophosphamide, procarbazine, transplantation for relapse
Non-Hodgkin lymphoma (intermediate and high grade)	**Combination chemotherapy:** Cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab (CHOP-R)	**Combination chemotherapy second line:** Dexamethasone, cisplatin, cytarabine (DHAP)Etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP) Ifosfamide, carboplatin, etoposide (ICE)Mesna, ifosfamide, mitoxantrone, etoposide (MINE); transplantation for high risk or first relapse
Non-Hodgkin lymphoma	**Combination chemotherapy:** Fludarabine, cyclophosphamide,	^{131}I tositumomab, ^{90}Y ibritumomab tiuxetan, bendamustine,

Head and neck cancer	**Combination chemotherapy:** Cisplatin, fluorouracil or Paclitaxel, carboplatin or Docetaxel, cisplatin, fluorouracil or Cisplatin or cetuximab with radiation therapy	Hydroxyurea, bleomycin, methotrexate, cetuximab
Esophageal cancer	**Combination chemotherapy:** Cisplatin, fluorouracil	Paclitaxel, irinotecan, oxaliplatin, capecitabine, docetaxel, epirubicin
Uterine cancer	Progestins, tamoxifen, aromatase inhibitors or **Combination chemotherapy:** Cisplatin, doxorubicin, or Paclitaxel or Cisplatin, doxorubicin or Carboplatin, paclitaxel	Fluorouracil

Treatment choices for cancers responsive to systemic agents.		
Testicular cancer	**Combination chemotherapy:** Bleomycin, etoposide, cisplatin (BEP) or Cisplatin, etoposide (EP)	Vinblastine, ifosfamide, paclitaxel, mesna
Kidney cancer	Sunitinib or temsirolimus or bevacizumab or sorafenib, or interleukin-2	Interferon-α, vinblastine, capecitabine, fluorouracil
Bladder cancer	**Combination chemotherapy:** Gemcitabine, cisplatin	Carboplatin, paclitaxel, docetaxel, fluorouracil, pemetrexed, methotrexate
Prostate cancer	Luteinizing hormone-releasing agonist (leuprolide, goserelin, triptorelin) plus an antiandrogen (flutamide, bicalutamide, nilutamide)	Ketoconazole, docetaxel, mitoxantrone, estramustine, prednisone
Thyroid cancer	Radioiodine (^{131}I) or sorafenib	Doxorubicin, dacarbazine
Adrenal cancer	Mitotane	Doxorubicin, etoposide, cisplatin
Stomach cancer	**Combination chemotherapy:** Epirubicin, cisplatin, fluorouracil or Docetaxel, cisplatin, fluorouracil or Fluorouracil, leucovorin, oxaliplatin	Capecitabine, sorafenib

1.1.1 1.8: Dose Calculations:

Chemotherapy medicine doses are often given as the amount of drug per Body Surface Area, or BSA(Fouad, 2018; Iannessi, Beaumont, Hebert, Dittlot, & Falewee, 2018). The formula which is used to calculate the body surface area is as follows.

$$BSA = \sqrt{\frac{W \times H}{3600}}$$

While answer must be in m^2, Weight in kg and height in Cms.

1.9: Treatment protocols

Treatment protocols which are used to treat the disease depends upon nature and condition of patients, if a person is suffering from rectal cancer, he or she cannot be treated with the protocol which are used for the lungs cancer and vice versa(Iannessi et al., 2018). The protocol schedule should be followed with accurate time table so that proper therapeutically benefit achieved and takeover the disease.

These protocols vary from one another, organ to organ, having different duration of action and dilution mediums and cycles, cycles can be change according to the patient conditions. These protocols having the specific follow up time(Allen, 2018).

CHAPTER 2: Literature Review

A potential drug–drug interaction (PDDI) is the incidence of a possibly harmful combination of prescribed drugs, rather than the occurrence of a real unwanted/ adverse event for a patient. There are various factors influencing the incidence of DDIs, some of them are pharmaceuticals, pharmacokinetic or pharmacodynamic mechanisms, which can have different consequences either increasing or decreasing the therapeutic effect, inducing adverse responses, or resulting in a response that does not occur when either agent is administered alone(Back et al., 1988). Food, formulation excipients, nutritional supplements and environmental factors such as cigarette smoking are among some common factors that can alter the pharmacokinetics and/or pharmacodynamics of medications(Goldberg, Mabee, Chan, & Wong, 1996).

Drug–drug interactions in cancer patients can possibly be the cause of death in up to 4% of patients, particularly those who are given drugs systemically are at higher risk for drug–drug interactions. Typically, cancer patients receive a high number of drugs concomitantly, these may comprise of cytotoxic agents, hormonal agents, targeted drug delivery systems, and supportive care agents are among medication prescribed to treat comorbidities. An additional problem is that the mean age of cancer patients is increasing(Bergamo, Dyson, & Sava, 2018; Money & Garber, 2018).

The significance of identification and management of DDIs in cancer sufferers is more due to the fact in addition to the impact of DDI on treatment goals, they can have devastating effects upon accuracy and validity of data collected within the clinical trial. By growing occurrence of ADRs due to amplified toxicity potential or decrease efficacy the DDI can highly impact data validly(McFeely, Wu, Ritchie, & Unadkat, 2018).

To conclude the prevalence in cancer patients negligible investigations have been carried out to discover whether the present DDI screening practices are sufficient or not. In cancer patients glucocorticoids such as dexamethasone are widely used to manage chemotherapy –induced emesis, they are well tolerated and effective antiemetics. They are used as solitary agent in mild emetogenic chemotherapy, in combination with 5-HT3 receptor antagonist in moderately emetogenic chemotherapy & in triple combination with 5-HT3 receptor antagonist and NK1 receptor antagonist in highly emetogenic chemotherapy(Datta, 2018).

For delayed prophylaxis glucocorticoids are efficient with both cisplatin and non-cisplatin-based chemotherapy. As a matter of fact one of the most extensively evaluated and used steroid is

dexamethasone.

It is estimated that about 60% of the cancer victims undergoing chemotherapy may develop at least one DDI which require 30% of medical intervention(Umar, 2018). Due to gap in effective professional communication between medical oncologist, clinical pharmacist and the nurse a majority of these drug-drug interaction are ignored and not given appropriate intervention. In order to rationalize the drug therapy and to improve patient care it is necessary to screen the potential drug-drug interactions before initiating chemotherapy. Hence, the present study was aimed to assess the patterns of pDDIs in the oncology unit of a tertiary care teaching hospital of Karachi, Pakistan.

Pharmacodynamic interactions result by administering two drugs having similar mechanisms of action (in which case they may behave in synergistic, additive, or antagonistic fashion) or when the pharmacological effect of one drug is altered by electrolytic abnormality induced by another drug. When a drug alters the absorption, metabolism, distribution and elimination the pharmacokinetic interaction takes place. Pharmacokinetic interactions caused by metabolic effects occur via drug interactions with cytochrome P450 enzymes along with antineoplastic medications including cyclophosphamide, taxanes, etoposide, irinotecan, aromatase inhibitors, vinca alkaloids, bicalutamide, imatinib, gefitinib, and erlotinib are metabolized by enzymes. . Incompatible dr ugs when mixed together demonstrate pharmaceutical interaction where two chemically incompatible drugs compounded as intra venous admixture before i.v administration resulting in inactivation of one or both drugs due to chemical/physical incompatibility (Devanathan et al., 2019). Due to difference in the design of research studies, the pDDI are prevailing in hospitals settings in a highly variable pattern. A study has been done in UK where two hospitals were compared. The significant findings showed that approximately 65% hospital admissions were cause by medicines, of which nearly 16.6% are due to drug interactions.

It is realized that 17% of the adverse drug reactions are due to drug-drug interaction. Almost dozens of DIs involving anticancer drugs are displayed in available databases and reviews. Example cotrimoxazole or pantoprazole may increase the toxicity of methotrexate, and even fatal cases of fluorouracil toxicity have been reported in patients who receive sorivudine or non sorivudine anti-inflammatory drugs (Sivapalarajah et al., 2018).

With a remarkable increase in available therapeutic options and their potentials to prolong life span of cancer patients. Clinical conclusion from such unfavorable drug-drug interaction is not

studied extensively in oncology. There are less than 10 reported studies which depict the frequency of drug-drug interactions in cancer chemotherapy. It is therefore very important to determine that how frequent are the patients undergoing chemotherapy exposed to the threat of real or potential DDIs.

In short it is examined that the exponential increase in the number of new treatment action option in oncology is likely to make DDI even more frequent threat, the expansion of institutional strategies to minimize these risk, hidden risks to put off damage to patients welfare(Hauben, Reynolds, & Caubel, 2018).

With a remarkable increase in the available therapeutic options and their potential to prolong life expectancy of cancer patients, the incidence of drug-drug interactions in oncology is becoming more common. However, clinical outcomes from such adverse drug events have not been extensively studied in oncology, with many studies reporting isolated cases, small series or single-institution experiences. There are less than 10 reported studies which depict the frequency of drug-drug interactions in cancer chemotherapy. It is therefore very important to determine that how frequent are the patients undergoing chemotherapy exposed to the threat of real or potential DDIs.

In summary, the exponential growth in the number of new treatment options in oncology is likely to make DDI an even more frequent threat. The knowledge of potential drug interactions in patients that commonly are exposed to polypharmacy, and the development of institutional strategies to minimize these hidden risks are necessary to prevent damage to patient's wellbeing.

Future studies should focus on better identification of real DDI and to develop prevention strategies to minimize the risk of DDI(Olin, Klibanov, Chan, & Spooner, 2019).

CHAPTER 3: Methodology

A prospective cross-sectional study was carried out for 3-month period (from March 2018 to May 2108) in the inpatient unit of oncology ward at Jinnah Postgraduate Medical Centre, Karachi. Before starting the study, the study protocol was approved by the Institutional Ethical Committee (meeting dated 05-03-2018). The patients from either gender with age >18 years and diagnosed with solid tumor or hematological malignancy were included in the study. Patients who referred to oncology department for consultation, patients who are not willing to participate, pregnant and lactating women or those who have had surgical resection of tumor or undergone any sort of radiotherapy recently were excluded from the study.

The data were collected from patient's treatment chart. Patient medication details were noted on the daily basis and recorded in the drug interactions documentation Performa. The pDDIs were those not observed in the patients, but they give a signal for the detection of interactions. Medscape multidrug interaction checker tool were used to identify the pattern of pDDIs. On entering the drugs one by one, the program lists the possible interactions and categorizes interactions according to their interaction effect, severity (major, moderate, and minor). Medscape contain a separate tool for detecting interactions known as the multidrug interaction checker tool. On entering the drugs one by one, the program lists the possible interactions and categorizes interactions according to their interaction effect, severity (major, moderate, and minor), and management. The required guidance to manage particular pDDI was provided to the physician by referring information provided in drug interaction tools. For progressively relevant data standard books like stockleys's medication connection. American wellbeing framework model medication data were alluded.

All agents of anticancer for malignant growth were considered, independent of the sort of agent (e.g. monoclonal antibodies and protein kinase inhibitors were additionally included), administration route (i.e., intravenous just as oral specialists were considered) and administration day. Potential medication sedate collaborations (drug-drug interaction) among medications and over the counter meds were not considered. At the point when drug formulation contained at least two pharmacologically dynamic fixings each medication was included exclusively the examination (e.g. tramadol/acetaminophen). Be that as it may, when a patient was taking a

similar medicine in more than one plan (e.g., long-and short-acting morphine) the medication was tallied just once.

Statistical Analysis

Descriptive statistics was used to describe the demographic characteristic of patients, type of cancer, treatment, the medications were used as per prescription, other serious diseases and classification of interactions between the drugs. All data was entered in SPSS version 2.1.Quantitative valuables like age, BSA, no. of chemo cycles received are presented as Mean standard deviation. Qualitative variables such as gender, tumor type, comorbidities are presented as frequency and percentages.

Potential Drug interactions in chemotherapy with respect to standard guidelines (Devita, Laxi, Medscape).

Demographic data

Name: _____

Age: _____ years

Gender: _____

Martial status: _____

Disease

S/NO	Durg	Dosage & dilution	Route of Administration	Interaction	Severity

By Pharmacist _____ Consultant _____

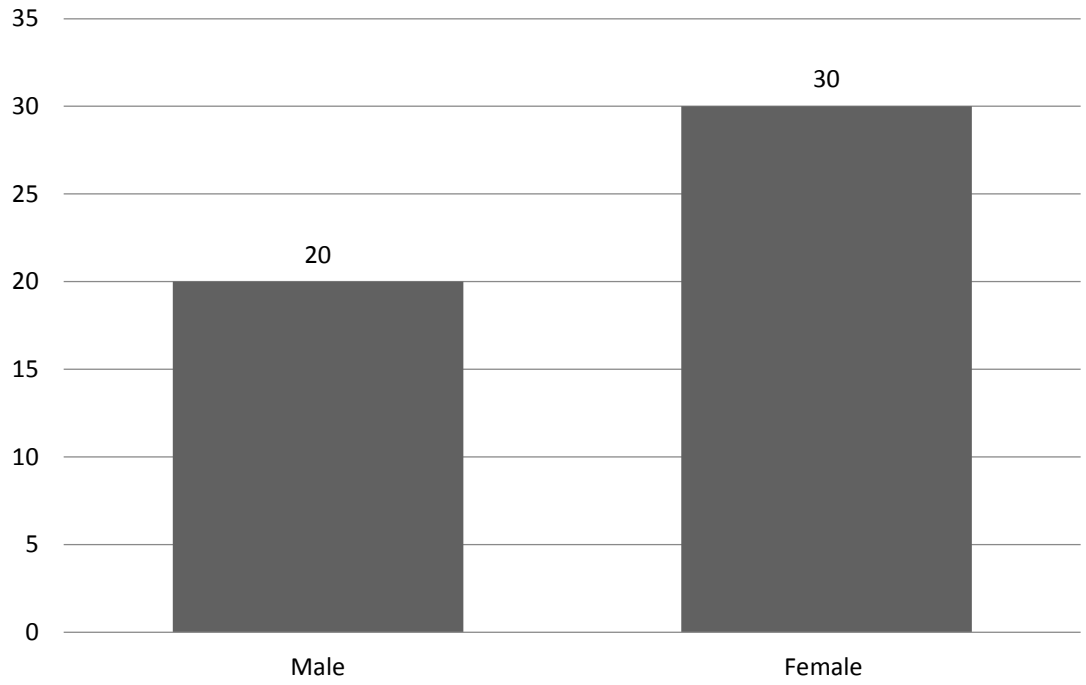
CHAPTER 4: Results

4.1 Patient demographic data:

Table and figure 4.1 demonstrate Patient demographic data. The total number of patients were 50 among which 20 patients are male while 30 patients were female.

Characteristics	No of patients	Percent of total
All patients	50	100%
Male	20	40%
Female	30	60%

Table: 4.1 Patient demographic data



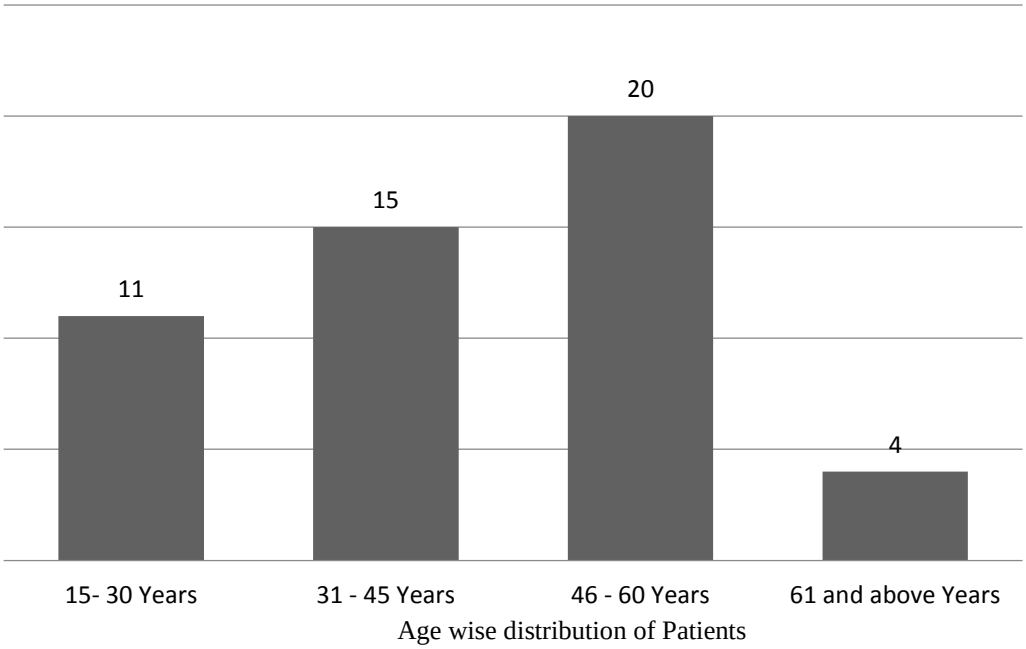
Gender-wise distribution

4.2 Age in years:

Table and figure 4.2 demonstrate the age wise distribution of all the patients. The highest number of patients were from the age group 46- 60 Years which amounted up to 40% of the total sample whereas, the least number of patients were from the group of 61-75 Years.

Table: 4.2 Age in years

Age in years	No of patients	Percent of total
15-30	11	22%
31-45	15	30%
46-60	20	42%
61 and above ~~– 75~~	4	8%



Age wise distribution of Patients

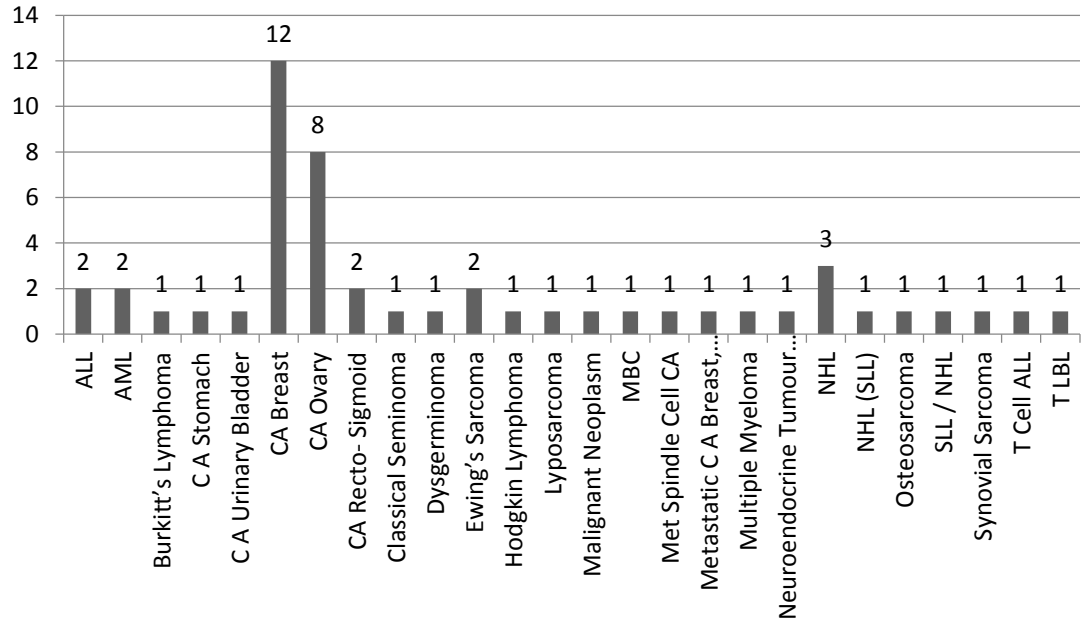
4.3 Cause of hospitalization:

Table and figure4.3 demonstrate that the cause of hospitalization with respect to the type of cancer present in the individual patient. The highest incidence was observed for CA Breast and CA Ovary being 28% and 20% of the sample size, simultaneously. Another significant finding was the presence of Non-Hodgkin Lymphoma which was seen in 7 patients, being 14% of the sample.

Cause of hospitalization	No of patients	Percent of total
Rectal Cancer	1	2%
Acute Lymphoblastic Leukemia (ALL)	2	4%
Acute Myeloid Leukemia (AML)	2	4%
Burkit's Lymphoma	1	2%
CA Beast	14	28%
CA Ovary	10	20%
Dysgerminoma	1	2%
Ewing's Sarcoma	2	4%
Met Spindle Cell CA	1	2%
MBC	1	2%
Lyposarcoma	1	2%
Multiple Myeloma	1	2%
Synovial Sarcoma	1	2%
Non Hodgkin Lymphoma	7	14%
Hodgkin Lymphoma	1	2%
Lymphoblastic Lymphoma (LBL)	1	2%

Neuro Endocrine Cancer	1	2%
Testicular Cancer	1	2%
Osteosarcoma	1	2%

Table: 3.3 Cause of Hospitalization



Cause of Hospitalization

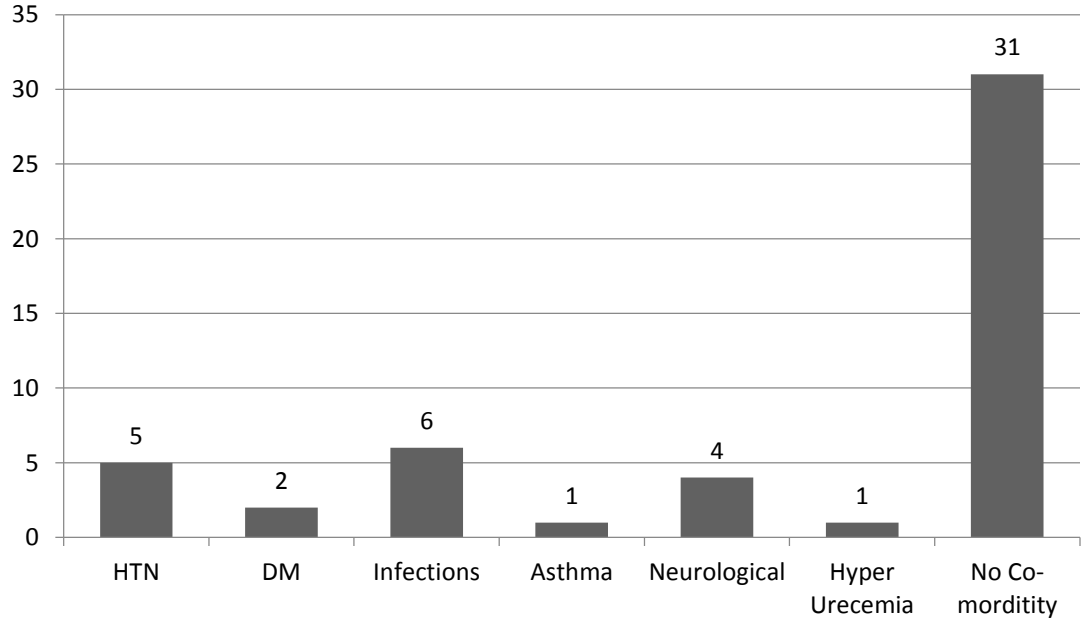
4.4 Concurrent diseases:

Table and figure 4.4 demonstrates patient suffering from concurrent diseases in addition to the cancer. 19 patients were identified having co-morbidities in which the highest occurrence was the infections which were seen in 6 individuals. This was followed by Hypertension and neurological disorders present in 5 and 4 patients simultaneously.

Table: 4.4 Concurrent diseases

Concurrent diseases	**No of patients**	**Percent of total**
Hypertension	5	10%

Neuronal Disorders	4	8%
Diabetes Mellitus	2	4%
Infections	6	12%
Hyper uricemia	1	2%
Asthma	1	2%
Patients without any Co-morbidities	31	62%



Cancer Patients with Co-morbidities

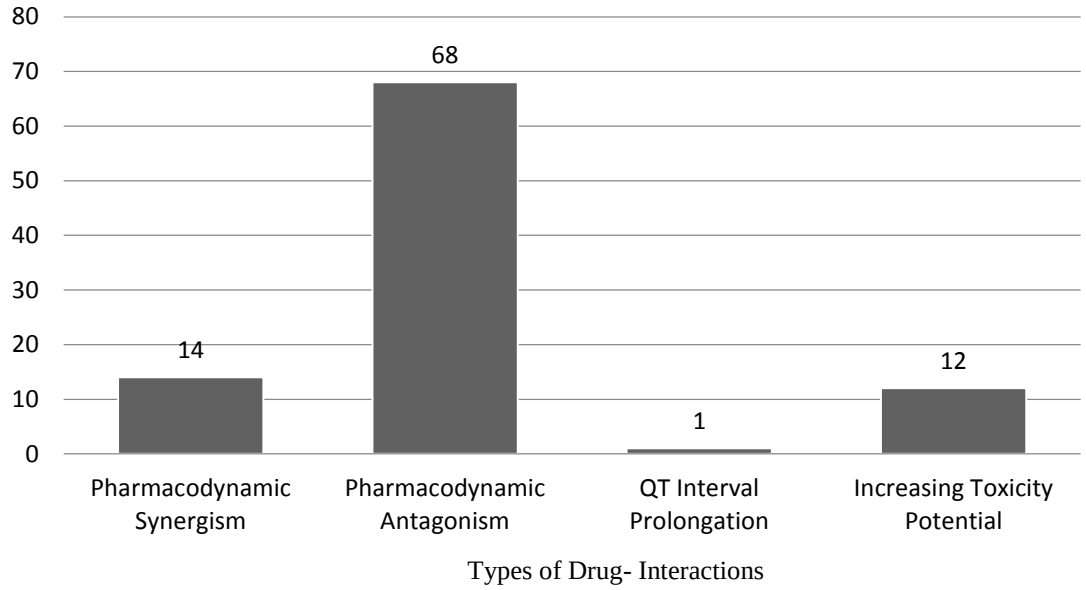
Types of Drug- Interactions:

Table No: 4.5 Frequency of Types of Drug- Interactions.

Table and figure 4.5demonstrates the class of drug interaction observed during the study. The highest incidence was that of antagonistic drug interactions which were seen in 71% of cases. On the other hand, only a single case of conduction problem in CVS was seen.

Table No: 4.5 frequency of drug related problem

Types of Drug Interactions	Frequency	Percentage
Pharmacodynamic Synergism	14	14%
Pharmacodynamic Antagonism	68	71%
QT Interval Prolongation	1	1%
Increasing Toxicity Potential	12	12%
Total drug interactions	95	100%



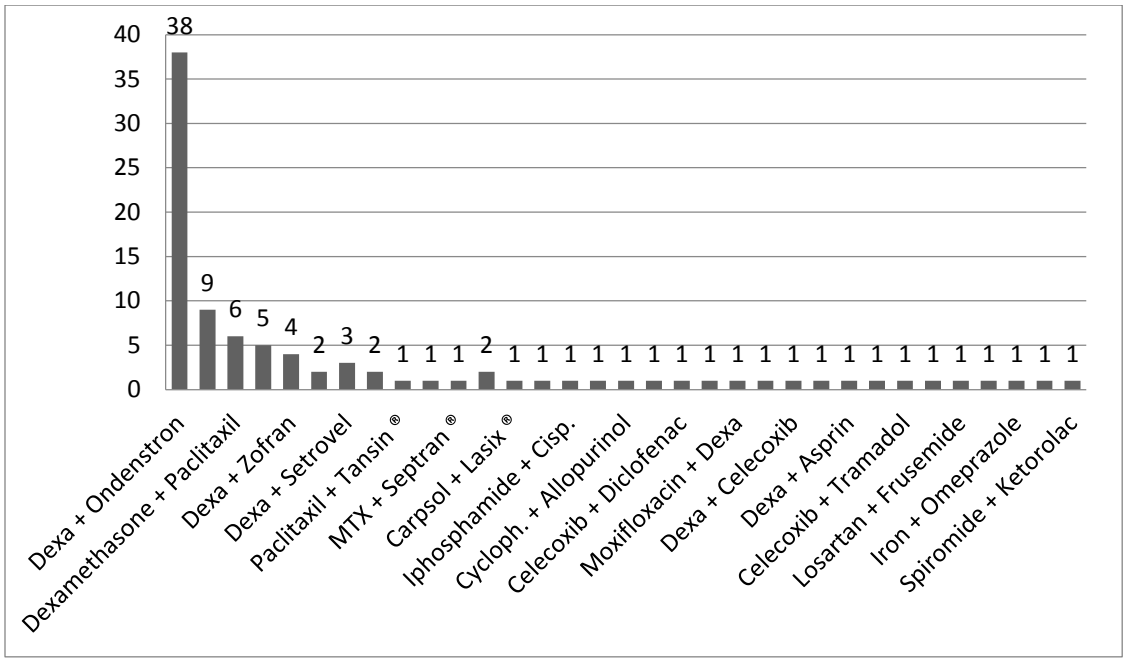
4.6 Drug Interactions (for individual drugs)

Table and figure 4.6 gives a comprehensive detail of the individual drug interaction that was observed in the pool of 50 hospitalized cancer patients. The interaction found in the 40% of population was between Dexamethasone and Ondenstron. There were 95 different interactions recorded in which 3 were of serious nature whereas the remaining were having moderate nature.

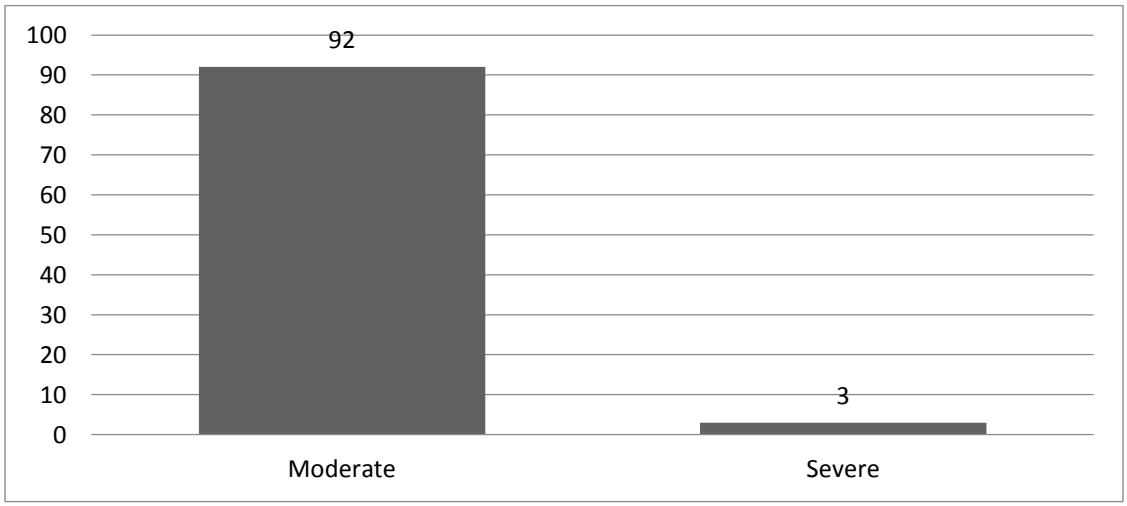
Table: 4.6 Drug interactions of each drug

Drug interactions	Occurrence	Percentage	Classification
Dexamethasone + Ondenstron	38	40%	Moderate
Dexamethasone + Doxorubicin	9	9%	Moderate
Dexamethasone + Paclitaxil	6	6%	Moderate
Dexamethasone + Etoposide	5	5%	Moderate
Dexamethasone + Zofran	4	4%	Moderate
Paclitaxil + Herceptin ®	2	2%	Moderate
Dexamethasone + Setrovel	3	3%	Moderate
Paclitaxil + Spiromide ®	2	2%	Moderate
Paclitaxil + Tansin ®	1	1%	Moderate
Methotrexate + Esomeprazole	1	1%	Moderate
Methotrexate + Septran ®	1	1%	Serious
Doxorubicin + Cyclophosphamide	2	2%	Moderate
Carpsol + Lasix ®	1	1%	Moderate
Bendumastine + Omeprazole	1	1%	Moderate
Iphosphamide + Cisplatin	1	1%	Moderate
Bortezumab + Dexamethasone	1	1%	Moderate
Cyclophosphamide + Allopurinol	1	1%	Moderate
Ironotecan + Dexamethasone	1	1%	Moderate
Celecoxib + Diclofenac Sodium	1	1%	Moderate
Moxifloxacin + Onset	1	1%	Serious
Moxifloxacin + Dexamethasone	1	1%	Moderate
Moxifloxacin + Iron	1	1%	Serious
Dexamethasone + Celecoxib	1	1%	Moderate
Dexamethasone + Tramadol	1	1%	Moderate
Dexamethasone + Asprin	1	1%	Moderate
Dexamethasone + Spiromide	1	1%	Moderate
Celecoxib + Tramadol	1	1%	Moderate
Avil + Gravinate	1	1%	Moderate
Losartan + Frusemide	1	1%	Moderate
Losartan + Omeprazole	1	1%	Moderate
Iron + Omeprazole	1	1%	Moderate
Iron + Ranitidine	1	1%	Moderate

Spiromide + Ketorolac	1	1%	Moderate
Total drug interactions	95	100%	



Types of Drug Interactions



Nature of Drug - Interactions

DISCUSSION

Drug–drug interactions in cancer patients can possibly be the cause of death in up to 4% of patients, particularly those who are given drugs systemically are at higher risk for drug–drug interactions. Typically, cancer patients receive a high number of drugs concomitantly, these may comprise of cytotoxic agents, hormonal agents, targeted drug delivery systems, and supportive care agents are among medication prescribed to treat comorbidities. An additional problem is that the mean age of cancer patients is increasing(Bergamo, Dyson, & Sava, 2018; Money & Garber, 2018).

A prospective cross-sectional study was carried out to study the impact of potential drug-drug interactions on the delivery and quality of care at the hospital setting. Given the observational nature of the study, the confounding factors could not be strictly controlled.

The major outcome of interest was the 95 different interactions recorded in a sample of 50 hospitalized cancer patients. The interaction found in the 40% of population was between Dexamethasone and Ondenstron. There were which 3 were of serious nature whereas the remaining were having moderate nature. The highest incidence with respect to the type of cancer was observed in CA Breast and CA Ovary being 28% and 20% of the sample size, simultaneously. Another significant finding was the presence of Non-Hodgkin Lymphoma which was seen in 7 patients, being 14% of the sample.

As far as patients suffering from concurrent diseases in addition to the cancer are concerned, the study revealed that 19 patients were identified having co-morbidities in which the highest occurrence was the infections which were seen in 6 individuals. This was followed by Hypertension and neurological disorders present in 5 and 4 patients simultaneously.

The results from our study are consistent with the trends indicated in the previous studies by McFreely et al. The authors shared similar experience with the incidence of potential drug-drug interactions in hospitalized patients.

CONCLUSION

The results of our prospective cross-sectional study indicate that patients receiving cytotoxic medicine for cancer chemotherapy at hospital have a significant potential risk of encountering a drug-drug interaction.

Taking into account the critical health condition and high cost of drug, the author strongly recommends that a system of prescription screening for drug-drug interactions may be developed/ established at tertiary care hospitals offering cancer chemotherapy. This will greatly enhance the delivery of quality care to the cancer patients on one hand while saving a lot of health capital on the other, which can be otherwise lost due to wastage of drug.

There is a strong need of conducting high quality randomized control trials to access the potential drug-drug interactions while balancing the confounding factors highlighted in the study.

REFERENCES

Ahles, T. A., & Root, J. C. (2018). Cognitive effects of cancer and cancer treatments. *Annual review of clinical psychology, 14*, 425-451.

Allen, B. (2018). Dose Determination for Hydrophilic and Lipophilic Drugs for Chemotherapy and Immunotherapy. *SM J Clin Trials, 1*(1), 1001.

Ashvitha, K., ShilpaAarthi, M., Thamizhkkanal, M., Rajendiran, M., & Malathi, S. (2018). *Hybrid Segmentation and 3D Modeling of Pleural Effusion on CT.* Paper presented at the International Conference for Phoenixes on Emerging Current Trends in Engineering and Management (PECTEAM 2018).

Babu, M. S., & Vijayalakshmi, V. (2019). A review on acute/sub-acute ischemic stroke lesion segmentation and registration challenges. *Multimedia Tools and Applications, 78*(2), 2481-2506.

Back, D., Grimmer, S., Orme, M., Proudlove, C., Mann, R., & Breckenridge, A. (1988). Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive- drug interactions with anticonvulsants and antibiotics. *British journal of clinical pharmacology, 25*(5), 527-532.

Balasubramanian, M., Fratzl- Zelman, N., O'Sullivan, R., Bull, M., FA Peel, N., Pollitt, R. C., . . . Roschger, P. (2018). Novel PLS3 variants in X- linked osteoporosis: Exploring bone material properties. *American Journal of Medical Genetics Part A, 176*(7), 1578-1586.

Bergamo, A., Dyson, P. J., & Sava, G. (2018). The mechanism of tumour cell death by metal-based anticancer drugs is not only a matter of DNA interactions. *Coordination Chemistry Reviews, 360*, 17-33.

Blanks, R. G., Wallis, M. G., Alison, R., Kearins, O., Jenkins, J., Patnick, J., & Given-Wilson, R. M. (2018). Impact of digital mammography on cancer detection and recall rates: 11.3 million screening episodes in the English National Health Service Breast Cancer Screening Program. *Radiology*, 181426.

Burkheimer, E., Starks, L., Khan, M., Oostendorp, L., Melnik, M. K., Chung, M. H., & Wright, G. P. (2018). The impact of obesity on treatment choices and outcomes in operable breast cancer. *The American Journal of Surgery*.

Cao, H., Bernard, S., Heutte, L., & Sabourin, R. (2018). *Improve the performance of transfer learning without fine-tuning using dissimilarity-based multi-view learning for breast cancer histology images.* Paper presented at the International Conference Image Analysis and Recognition.

Castellucci, P., Nanni, C., & Ambrosini, V. (2018). *Nuclear medicine imaging of prostate cancer in the elderly*. Paper presented at the Seminars in nuclear medicine.

Chandran, M. (2018). Primary Hyperparathyroidism *Evidence-Based Endocrine Surgery* (pp. 217-233): Springer.

Datta, S. P. A. (2018). Unleashing the new Wealth Of Nations. *Journal of Innovation Management, 6*(2), 13-37.

Devanathan, A. S., Anderson, D. J., Cottrell, M. L., Burgunder, E. M., Saunders, A. C., & Kashuba, A. D. (2019). Contemporary Drug- Drug Interactions in HIV Treatment. *Clinical Pharmacology & Therapeutics*.

Douglas, C. E., Henson, R., Drope, J., & Wender, R. C. (2018). The American Cancer Society public health statement on eliminating combustible tobacco use in the United States. *CA: a cancer journal for clinicians*.

Fouad, A. H. M. (2018). Value of Personalized Chemotherapy Dose adjustment in patients with Advanced Head and Neck cancer. *CU Theses*.

Goldberg, R. M., Mabee, J., Chan, L., & Wong, S. (1996). Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. *The American journal of emergency medicine*, *14*(5), 447-450.

Goodin, S. (2018). Pharmacists' critical role in cancer clinical trials: ASHP.

Guo, R., Lu, G., Qin, B., & Fei, B. (2018). Ultrasound imaging technologies for breast cancer detection and management: a review. *Ultrasound in medicine & biology*, *44*(1), 37-70.

Hamoen, E. H. J., Hoeks, C. M., Somford, D. M., van Oort, I. M., Vergunst, H., Oddens, J. R., . . . Rovers, M. M. (2018). Value of Serial Multiparametric Magnetic Resonance Imaging and Magnetic Resonance Imaging–guided Biopsies in Men with Low-risk Prostate Cancer on Active Surveillance After 1 Yr Follow-up. *European urology focus*.

Hauben, M., Reynolds, R., & Caubel, P. (2018). Deconstructing the pharmacovigilance hype cycle. *Clinical therapeutics*, *40*(12), 1981-1990. e1983.

Hesketh, R. L., & Brindle, K. M. (2018). Magnetic resonance imaging of cancer metabolism with hyperpolarized 13C-labeled cell metabolites. *Current opinion in chemical biology*, *45*, 187-194.

Iannessi, A., Beaumont, H., Hebert, C., Dittlot, C., & Falewee, M. N. (2018). Computer tomography-based body surface area evaluation for drug dosage: Quantitative radiology versus anthropomorphic evaluation. *PloS one*, *13*(2), e0192124.

Idrees, R., Fatima, S., Abdul-Ghafar, J., Raheem, A., & Ahmad, Z. (2018). Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. *World journal of surgical oncology*, *16*(1), 129.

Jabir, N. R., Firoz, C. K., Bhushan, A., Tabrez, S., & Kamal, M. A. (2018). The Use of Azoles Containing Natural Products in Cancer Prevention and Treatment: An Overview. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, *18*(1), 6-14.

Janiszewska, M., Raczkowski, M., Walczak, J., Składowski, K., & Maciejczyk, A. (2018). The Physical and Clinical Aspects of Radiation Therapy in Skin Cancer and Subcutaneous Tissue Neoplasm. *Health*, *10*(06), 730.

Juul, J. S., Hornung, N., Andersen, B., Laurberg, S., Olesen, F., & Vedsted, P. (2018). The value of using the faecal immunochemical test in general practice on patients presenting with non-alarm symptoms of colorectal cancer. *British journal of cancer*, *119*(4), 471.

Kaarthik, K., & Vivek, C. (2018). Lung Cancer Investigation Through Various Filters Using CT Images. *Current Trends In Biomedical Communication And Tele–Medicine*, 120.

Khwankong, S., Sriplung, H., & Kerdpon, D. (2018). Knowledge and Health belief attitudes of oral cancer and its screening among at-risk southern Thai Muslims. *Journal of Cancer Education*, *33*(3), 615-621.

Kim, E., Mema, E., Axelrod, D., Sigmund, E., Kim, S. G., Babb, J., & Melsaether, A. N. (2019). Preliminary analysis: Background parenchymal 18F-FDG uptake in breast cancer patients appears to correlate with background parenchymal enhancement and to vary by distance from the index cancer. *European journal of radiology*, *110*, 163-168.

Kishino, T., Okano, K., Ando, Y., Suto, H., Asano, E., Oshima, M., . . . Masaki, T. (2018). Esophageal cancer associated with a sarcoid-like reaction and systemic sarcoidosis in lymph nodes: supportive findings of [18F]-fluorodeoxyglucose positron emission tomography–computed tomography during neoadjuvant therapy. *Surgical case reports, 4*(1), 62.

Kuhl, C. K. (2019). Abbreviated Magnetic Resonance Imaging (MRI) for Breast Cancer Screening: Rationale, Concept, and Transfer to Clinical Practice. *Annual review of medicine, 70*, 501-519.

Kumar, A. (2018). Study of Depth-dose Distributions and Fragmentation Cross Sections of Heavy Ions using Geant4.

Lee, R., & Fredrick, D. (2015). Pediatric eye injuries due to nonpowder guns in the United States, 2002-2012. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 19*(2), 163-168. e161.

Lee, S., Kim, J. S., Ko, K. R., Lee, G. H., Lee, D. J., wook Kim, D., . . . Im, S. (2018). Direct Thermal Growth of Large Scale Cl-doped CdTe Film for Low Voltage High Resolution X-ray Image Sensor. *Scientific reports, 8*(1), 14810.

Li, X., Sun, W., Zhao, L., & Cai, J. (2019). Emission characterization of particulate matter in the ironmaking process. *Environmental technology, 40*(3), 282-292.

Lun, M. C., & Li, C. (2018). *X-ray luminescence imaging of water, air, and tissue phantoms.* Paper presented at the Multimodal Biomedical Imaging XIII.

Ma, K. W., Cheung, T. T., She, W. H., Chok, K. S. H., Chan, A. C. Y., Dai, W. C., . . . Lo, C. M. (2018). Diagnostic and prognostic role of 18-FDG PET/CT in the management of resectable biliary tract cancer. *World journal of surgery, 42*(3), 823-834.

McFeely, S. J., Wu, L., Ritchie, T. K., & Unadkat, J. (2018). Organic Anion Transporting Polypeptide 2B1–More Than a Glass-Full of Drug Interactions. *Pharmacology & therapeutics*.

Melsaether, A., Raad, R., Helbich, T., Moy, L., & Pinker, K. (2018). PET/MRI and Molecular Imaging in Breast Cancer *PET/MR Imaging: Current and Emerging Applications* (pp. 83-98): Springer.

Mishra, T., Mohan, M., Chakravarty, M., & Poddar, R. (2019). Zinc oxide nanoparticles (ZnONPs) as contrast agent for imaging of animal tissue using swept source optical coherence tomography (SSOCT). *Optik, 176*, 302-308.

Money, S., & Garber, B. (2018). Management of cancer pain. *Current Emergency and Hospital Medicine Reports, 6*(4), 141-146.

Nair, A. T., Ramachandran, V., Joghee, N. M., Antony, S., & Ramalingam, G. (2018). Gut Microbiota Dysfunction as Reliable Non-invasive Early Diagnostic Biomarkers in the Pathophysiology of Parkinson's Disease: A Critical Review. *Journal of neurogastroenterology and motility, 24*(1), 30.

Olin, J. L., Klibanov, O., Chan, A., & Spooner, L. M. (2019). Managing Pharmacotherapy in People Living With HIV and Concomitant Malignancy. *Annals of Pharmacotherapy*, 1060028019833038.

Olshansky, S. J., Passaro, D. J., Hershow, R. C., Layden, J., Carnes, B. A., Brody, J., . . . Ludwig, D. S. (2005). A potential decline in life expectancy in the United States in the 21st century. *New England Journal of Medicine, 352*(11), 1138-1145.

Organization, W. H. (2018). Informal advisory group on the availability and affordability of cancer medicines: report of the meeting 4-6 April 2018, Geneva, Switzerland: World Health Organ ization.

Patel, R., Zhang, L., Desai, A., Hoenerhoff, M. J., Kennedy, L. H., Radivoyevitch, T., . . . Welford, S. M. (2018). Mlh1 deficiency increases the risk of hematopoietic malignancy after simulated space radiation exposure. *Leukemia*.

Pizzi, A. D., Cianci, R., Genovesi, D., Esposito, G., Timpani, M., Tavoletta, A., . . . Rosa, C. (2018). Performance of diffusion-weighted magnetic resonance imaging at 3.0 T for early assessment of tumor response in locally advanced rectal cancer treated with preoperative chemoradiation therapy. *Abdominal Radiology, 43*(9), 2221-2230.

Rafiq, S., & Jeppesen, P. (2018). Is hypovitaminosis d related to incidence of type 2 diabetes and high fasting glucose level in healthy subjects: A systematic review and meta-analysis of observational studies. *Nutrients, 10*(1), 59.

Rahman, M. S., Suresh, S., & Waly, M. I. (2018). Risk Factors for Cancer: Genetic and Environment *Bioactive Components, Diet and Medical Treatment in Cancer Prevention* (pp. 1-23): Springer.

Rani, A. (2018). *A Modified Technique for Brain MRI Categorization Using 3-DGPR Method.*

Robertson, D. L. N. (2018). Pharmaceutical care of patients with cancer treated on non-cancer wards in the UK: a mixed methods study. *Eur J Hosp Pharm*, ejhpharm-2018-001662.

Selvanambi, R., Natarajan, J., Karuppiah, M., Islam, S. H., Hassan, M. M., & Fortino, G. (2018). Lung cancer prediction using higher-order recurrent neural network based on glowworm swarm optimization. *Neural Computing and Applications*, 1-14.

Shao, H., Ma, X., Gao, Y., Wang, J., Wu, J., Wang, B., . . . Tian, J. (2018). Comparison of the diagnostic efficiency for local recurrence of rectal cancer using CT, MRI, PET and PET-CT: A systematic review protocol. *Medicine, 97*(48).

Shiradkar, R., Ghose, S., Jambor, I., Taimen, P., Ettala, O., Purysko, A. S., & Madabhushi, A. (2018). Radiomic features from pretreatment biparametric MRI predict prostate cancer biochemical recurrence: preliminary findings. *Journal of Magnetic Resonance Imaging, 48*(6), 1626-1636.

Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics, 2015. *CA: a cancer journal for clinicians, 65*(1), 5-29.

Sivapalarajah, S., Krishnakumar, M., Bickerstaffe, H., Chan, Y., Clarkson, J., Hampden- Martin, A., . . . Pirmohamed, M. (2018). The prescribable drugs with efficacy in experimental epilepsies (PDE 3) database for drug repurposing research in epilepsy. *Epilepsia, 59*(2), 492-501.

Sulieman, A., Serhan, O., Al-Mohammed, H., Mahmoud, M., Alkhorayef, M., Alonazi, B., . . . Yousef, A. (2018). Estimation of cancer risks during mammography procedure in Saudi Arabia. *Saudi Journal of Biological Sciences*.

Umar, R. M. (2018). Drug-drug interactions between antiemetics used in cancer patients. *Journal of Oncological Sciences*.

Uqaili, A. A., Shah, R., ul Hussain, A., Kumar, N., Pauwels, E., Burkle, F. M., . . . Kuiken, T. (2018). Oral cancer awareness and Prevalence of Betel nuts, pan and ghutka in school children of rural areas of Sindh, Pakistan. *Ecological Informatics, 49*, 24.

Van Son, M. J., Peters, M., Moerland, M. A., Noteboom, J. L., Eppinga, W. S., Fajardo, R. D., & Lagendijk, J. (2018). Re-salvage MRI-guided Focal High-dose-rate Brachytherapy for Locally Recurrent Prostate Cancer. *Cureus, 10*(4).

Werner, R. A., Andree, C., Javadi, M. S., Lapa, C., Buck, A. K., Higuchi, T., . . . Pienta, K. J. (2018). A voice from the past: rediscovering the Virchow node with prostate-specific membrane antigen-targeted 18F-DCFPyL positron emission tomography imaging. *Urology, 117*, 18-21.

Yaffe, M. J., Mittmann, N., Alagoz, O., Trentham-Dietz, A., Tosteson, A. N., & Stout, N. K. (2018). The effect of mammography screening regimen on incidence-based breast cancer mortality. *Journal of medical screening, 25*(4), 197-204.

Zhang, W., Shu, P., Wang, S., Song, J., Liu, K., Wang, C., & Ran, L. (2018). ZNF154 is a promising diagnosis biomarker and predicts biochemical recurrence in prostate cancer. *Gene, 675*, 136-143.

Zitvogel, L., Ma, Y., Raoult, D., Kroemer, G., & Gajewski, T. F. (2018). The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies. *Science, 359*(6382), 1366-1370.