AN OBSERVATIONAL STUDY TO ASSESS THE SAFETY PROFILE OF TAXANES – DOCETAXEL AND PACLITAXEL IN CANCER PATIENTS

Dissertation submitted to Kerala University of Health Sciences

In partial fulfilment of the requirements for the award of the Degree of

DOCTOR OF PHARMACY

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MAY 2023

ABSTRACT

Cancer is a common and frequently occurring disease which seriously endangers human health. In the combat against cancer, natural compounds play a principal role. Taxanes mainly paclitaxel and docetaxel, the microtubule stabilizers, have been well known for the first line therapy, for cancers mainly breast and ovarian cancers.

The application of taxanes in clinical setting is characterized by severe side effects – hypersensitivity, neuropathy, edema. Effective monitoring of the ADR and the refinement of taxane is beneficial for cancer patients.

AIM

To conduct an ambispective observational study to assess the safety profile of Taxanes – Paclitaxel and Docetaxel in cancer patients.

OBJECTIVES

1. To analyse the prescribing pattern of Taxanes – Docetaxel and Paclitaxel.

2. To document safety profile of Taxanes – Docetaxel and Paclitaxel.

3. To identify drug interactions of Taxanes – Docetaxel and Paclitaxel with other drugs if any.

4. To analyse and compare the adverse effects of Paclitaxel and Docetaxel.

METHODOLOGY

STUDY DESIGN:

An Ambispective observational single centre study using medical records. The study population were based on the patient records of all cancer types receiving chemotherapy with Paclitaxel or Docetaxel.

DURATION OF STUDY:

A retrospective 2 years and prospective 6 months study from January 2021 to April 2023.

STUDY SETTINGS:

The study was conducted in the oncology department of Lourdes Hospital, Ernakulam which is a tertiary care teaching hospital. It is a 600 bedded multi-specialty tertiary care referral teaching hospital wide range of amenities. The institution is equipped with seven super specialty departments and 22 other department with facilities comprising twelve operation theaters, ten intensive care units and computerized Lourdes Mediware system clinical laboratories are with ISO standards. It is the one of the top most hospitals in Kerala.

SAMPLE SIZE:

The minimum sample size required for the study was calculated to be 49,

$n=(z^2pq)/m^2$

z=statistic corresponding to the level of confidence 1.96

p=expected prevalence = 85

q=(100-p) =15

m= allowable error=10

STUDY SAMPLE:

The patients were selected from oncology department who satisfied the inclusion and exclusion criteria.

INCLUSION CRITERIA:

1) Age ≥18 years.
2) Patients on chemotherapy with Paclitaxel or Docetaxel
3) All cancer types.

EXCLUSION CRITERIA:

Patients who got discharged against medical advice.

DATA COLLECTION TOOLS:

- Lourdes Mediware system.
- Specially designed data collection form.

- Patient's medical records.

STUDY METHOD:

We conducted an ambispective single centre observational study on cancer patients in oncology department of Lourdes Hospital, Ernakulam. The study period was from January 2021 to April 2023. Medical records of patients with all cancer types receiving chemotherapy with Paclitaxel or Docetaxel, admitted from 2021 onwards and who satisfied inclusion and exclusion criteria of the study were enrolled. A specially designed data collection form was prepared to collect the data. The patients who got discharged against the medical advice were excluded since the outcome measurement may not be clearly examined. The records of all patients enrolled in study were analysed and recorded in a specially designed data collection form. Demographics, past medical and medication history, reports of histopathology, ADR and side effects with management, treatment data, taxane prescribed with dose and concomitant drug details and pertinent lab parameters were recorded.

DESCRIPTIVE STATISTICAL ANALYSIS:

The collected data were compiled using Microsoft excel and were presented in graphical format using pie chart and bar graphs. Calculations of the mean and standard deviation were done using statistical calculators. The statistical software SPSS was used for analysis of the data.

1.INTRODUCTION

Cancer is a condition in which cells grow uncontrollably to form tumors, which are lumps of tissues and spread to other part of body. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. The most common cancers are breast, lung, colon and rectum and prostate cancers.[1]

Cancer cells develop because of multiple changes in their genes. These changes can have many possible causes. Lifestyle habits, genes and being exposed to cancer-causing agents in the environment can all play a role. Many times, there is no obvious cause.[2]

The genetic changes that contribute to cancer tend to affect three main types of genes – Proto-Onco genes, tumor suppressor genes, and DNA repair genes. These changes are sometimes called "drivers" of cancer.

- Proto-oncogenes are involved in normal cell growth and division. However, when these genes are altered in certain ways or are more active than normal, they may become cancer-causing genes (or oncogenes), allowing cells to grow and survive when they should not.

- Tumor suppressor genes are also involved in controlling cell growth and division. Cells with certain alterations in tumor suppressor genes may divide in an uncontrolled manner.

- DNA repair genes are involved in fixing damaged DNA. Cells with mutations in these genes tend to develop additional mutations in other genes and changes in their chromosomes, such as duplications and deletions of chromosome parts. Together, these mutations may cause the cells to become cancerous.[3]

Cancer can be divided into four, based on its origin. It includes carcinomas, sarcomas, leukemias, lymphomas.

- **Carcinomas -** A carcinoma begins in the skin or the tissue that covers the surface of internal organs and glands. Carcinomas usually form solid tumors. They are the most

common type of cancer. Examples of carcinomas include prostate cancer, breast cancer, lung cancer, and colorectal cancer.

- **Sarcomas** - A sarcoma begins in the tissues that support and connect the body. A sarcoma can develop in fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone.
- **Leukemias** - Leukemia is a cancer of the blood. Leukemia begins when healthy blood cells change and grow uncontrollably. The 4 main types of leukemia are acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia.
- **Lymphomas.** Lymphoma is a cancer that begins in the lymphatic system. The lymphatic system is a network of vessels and glands that help fight infection. There are 2 main types of lymphomas: Hodgkin Lymphoma and Non-Hodgkin Lymphoma.[4]

Cancer arises from the transformation of normal cells into tumour cells in a multi-stage process that generally progresses from a pre-cancerous lesion to a malignant tumour. These changes are the result of the interaction between a person's genetic factors and three categories of external agents, including:

- Physical carcinogens, such as ultraviolet and ionizing radiation;
- Chemical carcinogens, such as asbestos, components of tobacco smoke, alcohol, aflatoxin (a food contaminant), and arsenic (a drinking water contaminant); and
- Biological carcinogens, such as infections from certain viruses, bacteria, or parasites.[1]

MANAGEMENT OF CANCER

SURGERY

Curative or primary surgery is usually done when cancer is found in only one part of the body, and it's likely that all of the cancer can be removed. It is called "curative" because the purpose of the surgery is to remove all of the cancer completely. In this case, surgery can be the main treatment. It may be used along with other treatments like chemotherapy or radiation therapy given before or after the operation, but surgery can also be used alone. Debulking surgery is used to remove some, but not all, of the cancer. It's called "debulking"

because the tumor being treated is a large, bulky object and might be located very close to important organs or tissues. So, "de-bulking" the tumor can help make it smaller. The palliative type of surgery is used to treat problems caused by advanced cancer. Palliative surgery can be used with other treatments to correct a problem that's causing discomfort or disability.[5]

RADIATION

Radiation therapy is a cancer treatment that uses high-energy x-ray or other particles to destroy cancer cells. A radiation therapy regimen, or schedule, usually consists of a specific number of treatments given over a set period. Radiation therapy can treat many different types of cancer. It can also be used in combination with other cancer treatments, such as chemotherapy and/or surgery. The most common type of radiation therapy is external-beam radiation therapy. It delivers radiation from a machine outside the body. It can be used to treat large areas of the body, if needed.

A machine called a linear accelerator, or linac, creates the radiation beam for x-ray or photon radiation therapy. Special computer software adjusts the beam's size and shape. This helps target the tumor while avoiding healthy tissue nearby.[6]

CHEMOTHERAPY

Chemotherapy is a systemic medication. There are many different kinds of chemotherapy. In general, drugs used for chemotherapy are powerful chemicals that treat cancer by attacking cells during specific parts of the cell cycle. All cells go through the cell cycle, which is how new cells are made. Cancer cells go through this process faster than normal cells, so chemotherapy has more of an effect on these fast-growing cells. Because chemotherapy travels through the whole body, it can also damage healthy cells as they go through their normal cell cycle. This is why chemotherapy can cause side effects like hair loss and nausea.[7]

TARGETED THERAPY

A targeted therapy can be used by itself or in combination with other treatments, such as traditional or standard chemotherapy, surgery, or radiation therapy.

Targeted therapy drugs interfere with specific molecules found in receptors or proteins, on and in cancer cells. The goal with targeted therapy is to stop or slow tumor growth by interfering or attacking the genetic features of the cells that regulate growth and division. Unlike immunotherapy, which stimulates a person's immune system to recognize cancer cells as foreign bodies and attack them, targeted therapy relies on the drugs it uses or carries to do the attacking.[8, 9]

TYPES OF TARGETTED THERAPY

1) Angiogenesis inhibitors: These block the formation of new blood vessels that feed and nourish the cancer cells. Example: bevacizumab

2)Monoclonal antibodies: These might deliver molecules by themselves or molecules with drugs into or onto the cancer cell to kill it. Examples: alemtuzumab (certain chronic leukemias), trastuzumab (certain breast cancers), cetuximab (certain colorectal, lung, head and neck cancers).

3)Proteasome inhibitors: These disrupt normal cell functions so the cancer cells die. Example: bortezomib (multiple myeloma)

4) Signal transduction inhibitors: These disrupt cell signals so that they change the actions of the cancer cell. Example: imatinib (certain chronic leukemias).[8]

IMMUNOTHERAPY

Immunotherapy is treatment that uses a person's own immune system to fight cancer. Immunotherapy can boost or change how the immune system works so it can find and attack cancer cells.[10]

TYPE OF IMMUNOTHERAPY

1) Checkpoint inhibitors: These drugs basically take the 'brakes' off the immune system, which helps it recognize and attack cancer cells.

2) Cytokines: This treatment uses cytokines to stimulate the immune cells to attack cancer.

3) Immunomodulators: This group of drugs generally boosts parts of the immune system to treat certain types of cancer.

4) Monoclonal antibodies: These are man-made versions of immune system proteins. mAbs can be very useful in treating cancer because they can be designed to attack a very specific part of a cancer cell.[11]

HORMONE THERAPY

Hormone therapy is considered a systemic treatment because the hormones they target circulate in the body. The drugs used in hormone therapy travel throughout the body to target and find the hormones. [12]

TAXANES

Taxanes are a class of chemotherapy drugs used to treat ovarian cancer, breast cancer and prostate cancer, among other cancer types. They prevent cell division, or mitosis, the process cancer cells use to make more cancer cells. They kill cancer cells and slow tumor growth. Taxanes include paclitaxel, docetaxel and cabazitaxel.[13]

One class of drugs commonly used in the treatment of breast cancer is the microtubule-stabilizing agents (MSAs) also known as microtubule inhibitors (MIs), namely paclitaxel and docetaxel. The commercially available taxanes, paclitaxel and docetaxel, have become widely recognized as extremely active chemotherapeutic agents in the treatment of breast cancer. The taxanes, paclitaxel and docetaxel are microtubule-stabilizing agents that function primarily by interfering with spindle microtubule dynamics causing cell cycle arrest and apoptosis. These drugs suppress microtubule (MT) dynamics by preferentially and reversibly binding to the β-subunit of the tubulin heterodimer. Microtubules are involved in a variety of cellular processes, such as signalling, migration, and division, that are critical for cancer cell proliferation and metastasis. By adding or removing tubulin subunits at the Microtubule ends, Microtubules can alternate between growth and shortening phases through their characteristic "dynamic instability" behaviour. Given that dynamic spindle Microtubules are vital for effective cell division, drugs that suppress Microtubule dynamic instability can be useful to prevent cancer cell proliferation. Binding of taxanes stimulates microtubule polymerization and induces the formation of stable MT bundles. This action alters the natural dynamics of MTs, prevents proper spindle formation, blocks mitosis and induces apoptosis[13, 14]

Paclitaxel and its semisynthetic analogue docetaxel exhibit significant antitumor activity.[15] Docetaxel differs from paclitaxel in two positions in its chemical structure and this small alteration makes it more water soluble. Although very active clinically, paclitaxel and docetaxel have several clinical problems including poor drug solubility, serious dose-limiting toxicities such as myelosuppression, peripheral sensory neuropathy, allergic reactions, and eventual development of drug resistance.[16]

DOCETAXEL

Microtubule-targeting agents as taxanes (docetaxel and paclitaxel) are widely used in treating advanced and metastatic cancers. Docetaxel, is a recently available anticancer agent of the taxane class.

Docetaxel is a semisynthetic product of 10-deacetylbaccatin III, isolated from Taxus baccata. Docetaxel promotes microtubule assembly and stabilizes microtubules while simultaneously preventing their depolymerization. Cells are arrested at the G2 /M transition, resulting in failed cell division and cytotoxicity.

Docetaxel is a more potent antimicrotubular agent than paclitaxel in vitro, and has also been shown to be active in a broad range of tumors including carcinomas of the lung, breast, bladder, pancreas, head and neck and ovary.

Docetaxel, a cytotoxic taxane, is an antimicrotubular agent effective in the treatment of patients with cancer. Although docetaxel is associated with neutropenia and other adverse events, its overall tolerability profile is generally acceptable in the majority of patients. Docetaxel, therefore, is an effective option in the treatment of patients with metastatic breast cancer after failure of prior chemotherapy.[13,16,17]

PHARMACOLOGICAL PROPERTIES

Docetaxel is an antimicrotubular agent that principally exerts its cytotoxic activity by promoting and stabilising microtubule assembly while simultaneously preventing microtubule depolymerization. This results in inhibition of normal cell division.

In vitro and in vivo, docetaxel has antineoplastic activity against a wide range of cancer cells, demonstrates synergistic activity with several antineoplastic agents and often has greater cytotoxic activity against human breast cancer cell lines than paclitaxel.

The pharmacokinetics of docetaxel are linear at clinically relevant doses and are consistent with a three-compartment model. Docetaxel is highly bound to plasma proteins, but has a large volume of distribution at steady state. It is primarily metabolised by the cytochrome P450 3A4 isoenzyme and is excreted primarily faecally via the biliary tract. Clearance of the drug is a strong independent predictor of severe hematological toxicity in cancer patients. Docetaxel is widely distributed in tissues with a mean volume of distribution of 74 L/m^2 after 100 mg/m^2, every 3 weeks. The mean total body clearance after this schedule is approximately 22 $L/h/m^2$, principally because of hepatic metabolism by the cytochrome P450 (CYP)3A4 system and biliary excretion into the faeces. Renal excretion is minimal (<5%). Docetaxel is >90% bound in plasma.[16]

PACLITAXEL

Paclitaxel is an antimicrotubular agent. It promotes the assembly of microtubules by enhancing the action of tubulin dimers and stabilizing current microtubules while inhibiting their disassembly. Due to the stability of the microtubules, the late G2 phase stops, and cell replication becomes inhibited. Paclitaxel may also distort mitotic spindles causing the chromosomes to break. Paclitaxel has a black box warning for hypersensitivity reactions and bone marrow suppression.[18]

PHARMACOLOGICAL PROPERTIES OF PACLITAXEL

Paclitaxel is a taxoid chemotherapeutic agent used as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary, and other various cancers including breast and lung cancer. Paclitaxel is 89%-98% bound to plasma protein. The presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine do not affect protein binding of paclitaxel. In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6a-hydrox-ypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6a, 3'-p-dihydroxypaclitaxel, by CYP3A4.[19]

MECHANISM OF ACTION OF TAXANES

Taxanes block cell cycle progression through centrosomal impairment, induction of abnormal spindles and suppression of spindle microtubule dynamics. Triggering of

apoptosis by aberrant mitosis or by subsequent multinucleated G1-like state related to mitotic slippage, depends on cell type and drug schedule. The development of fluorescent derivatives of paclitaxel led us to locate spindle pole microtubules and centrosomes as main sub-cellular targets of cytotoxic taxoids in living cells. [20]

Microtubules are important structural and functional components of the eukaryotic cytoskeleton. They are involved in cell division, migration, signalling, and intracellular trafficking and are important in cancer cell proliferation and metastasis.[20] The taxanes are microtubule-stabilizing drugs that enhance microtubule polymerization at high concentrations.[21] All taxanes bind to the same or to an overlapping taxoid-binding site on β-tubulin, located on the inner surface of the microtubule.[22]

MECHANISM OF RESISTANCE

Taxane resistance is multi-faceted and involves multiple pathways in proliferation, apoptosis, metabolism, and the transport of foreign substances.[23] Several mechanisms have been associated with paclitaxel resistance; one mechanism is the overexpression of the efflux protein P-glycoprotein, which increases the outflow of paclitaxel from the cells.[24] Another mechanism that contributes to this resistance is the overexpression of IκB kinase β (IKKβ), an upstream regulator of nuclear factor-κB (NF-κB) signaling[25]. Although several mechanisms of paclitaxel chemoresistance have been described, they are not completely understood.[26]

The transcription factor NF-κB family contains five members: NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), c-Rel and RelB. These transcription factors form homo- and hetero-dimers that under normal conditions reside in the cytoplasm bound to inhibitors, known as inhibitors of NF-κB (IκBs). The activation of NF-κB requires the IKK-dependent phosphorylation of IκBs (α, β and ε), which leads to polyubiquitination and subsequent degradation by the proteasome. Next, NF-κB is translocated to the nucleus where it regulates the expression of its target genes. NF-κB is activated by a wide variety of stimuli that include growth factors, cytokines, infectious agents and chemotherapy drugs, among others.[25] NF-κB is involved in the regulation of biological processes, such as proliferation, differentiation and apoptosis, and some pathologies, such as inflammation, cancer and chemotherapy resistance.[27] The epithelial-mesenchymal transition (EMT) is a biological process in which a polarized epithelial cell normally interacts with the basement membrane via its basal

surface, and undergoes a series of morphological and biochemical changes that allow it to adopt a mesenchymal phenotype.[28,29] This phenotype increases migratory capacity, invasiveness, resistance to apoptosis and the production of extracellular matrix components.[29] EMT is one of the multiple cellular processes that are regulated by NF-κB, since it also regulates the expression of SNAIL and Twist in breast, renal and colon cancer.[30] EMT is an early step of cancer metastasis. During EMT, cell morphology and shape are modified to gain motility/invasive features, epithelial markers such as E-cadherin are downregulated and cells acquire mesenchymal markers such as N-cadherin and vimentin; these changes are controlled by the transcription factors SNAIL, Twist and Slug.[31-33]

INDICATIONS

Table 1.1: Indications of Paclitaxel and Docetaxel.

PACLITAXEL	DOCETAXEL
Ovarian cancer	1. Breast cancer locally advanced or metastatic breast cancer after failure of prior chemotherapy.
Breast cancer	2. Breast cancer-adjuvant treatment of patients with node-positive breast cancer.
SCLC and NSCLC	3. NSCLC locally advanced or metastatic disease after failure of prior platinum-based chemotherapy.
Head and neck cancer	4. NSCLC-FDA-approved in combination with cisplatin for treatment of patients with locally advanced or metastatic disease who have not previously received chemotherapy.
Oesophageal cancer	5. Prostate cancer
Prostate cancer	6. Gastric cancer- in combination with cisplatin and 5-fluorouracil (5-FU) for advanced gastric cancer, including adenocarcinoma

	of the gastroesophageal junction, in patients who have not received prior chemotherapy.
Bladder cancer	7. Head and neck cancer- in combination with cisplatin and 5-FU for induction treatment of patients with inoperable, locally advanced disease.
AIDS-related Kaposi's sarcoma	8. SCLC.
	9. Refractory ovarian cancer.
	10. Bladder cancer.
	11. Breast cancer-FDA-approved for the treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy.[34]

DRUG INTERACTIONS

Because the taxanes undergo hepatic oxidation via the cytochrome p450 system, pharmacokinetic interactions due to enzyme induction or inhibition can occur.[35]

Interactions may occur when the taxanes paclitaxel and docetaxel are given concurrently with other drugs. Altered clearance may be expected because these agents are extensively metabolized by hepatic cytochrome P-450 enzymes, particularly isoenzymes 3A and 2C. Pharmacodynamic interactions that alter the molecular target or pharmacology of a drug may depend on the sequence or schedule of administration.[36]

In paclitaxel,

1. Radiation Therapy-Paclitaxel is a radio sensitizing agent.

2. Concomitant use of inhibitors and/or activators of the liver P450 CYP3A4 enzyme system may affect paclitaxel metabolism and its subsequent antitumor and toxic effects.

3. Phenytoin, phenobarbital-Accelerate the metabolism of paclitaxel, resulting in lower plasma levels of drug.

4. Cisplatin, carboplatin-Myelosuppression is greater when platinum compound is administered before paclitaxel. Platinum compounds inhibit plasma clearance of paclitaxel. When a platinum analogue is used in combination, paclitaxel must be given first.

5. Cyclophosphamide-Myelosuppression is greater when cyclophosphamide is administered before paclitaxel.

6. Doxorubicin-Paclitaxel reduces the plasma clearance of doxorubicin by about 30%, resulting in increased severity of myelosuppression.[34]

In docetaxel,

1. Radiation Therapy-Docetaxel acts as a radio sensitizing agent.

2. Inhibitors and/or activators of the liver cytochrome P450 CYP3A4 enzyme system-Concurrent use with drugs such as cyclosporine, ketoconazole, and erythromycin may affect docetaxel metabolism and its subsequent antitumor and toxic effects[34].

DOSAGE RANGE IN TAXANES

Table 1.2: Dosage range in Paclitaxel and Docetaxel.

PACLITAXEL	DOCETAXEL
Metastatic breast cancer-60, 75, and 100 mg/m² IV every 3 weeks or 35-40 mg/m² IV weekly for 3 weeks with 1-week rest.	1. Ovarian cancer: 135-175 mg/m² IV as 3-hour infusion every 3 weeks
Breast cancer-75 mg/m² IV every 3 weeks in combination with cyclophosphamide and doxorubicin for adjuvant therapy.	2. Breast cancer: 175 mg/m² as 3-hour infusion every 3 weeks

NSCLC-75 mg/m² IV every 3 weeks or 35-40 mg/m² IV weekly for 3 weeks with 1-week rest after platinum-based chemotherapy.	3 Bladder cancer, head and neck cancer, 250 mg/m as a 24-hour infusion every 3v 3 weeks
NSCLC-75 mg/m² IV every 3 weeks in combination with cisplatin in patients who have not received prior chemotherapy.	4 Weekly schedule: 80-100 mg/m2IV each week for 3 weeks with 1-weak rest
Metastatic prostate cancer-75 mg/m² IV every 3 weeks in combination with prednisone.	5 Infusional schedule 140 mg/m2as a 96-hour infusion[34]
Advanced gastric cancer-75 mg/m² IV every 3 weeks in combination with cisplatin and 5-FU.[34]	

TOXICITIES OF TAXANES

Table 1.3: Toxicities of Paclitaxel and Docetaxel.

PACLITAXEL	DOCETAXEL
1. Myelosuppression Dose-limiting neutropenia with nadir at day 8-10 and recovery by day 15-21. Decreased incidence of neutropenia with 3-hour schedule when compared to 24-hour schedule	1.Myelosuppression with neutropenia is dose-limiting. Nadir is usually observed at days 7-10, with recovery by day 14. Thrombocytopenia and anemia are also observed.
2. Infusion reactions Occurs in up to 20%-40% of patients Characterized by generalized skin rash, flushing, erythema, hypotension, dyspnoea, and/or bronchospasm Usually occurs within the first 2-3 minutes of an infusion and almost always within the first 10 minutes Incidence of hypersensitivity reaction is the same with	2.Hypersensitivity reactions with generalized skin rash, erythema, hypotension, dyspnea, and/or bronchospasm. Usually occur within the first 2-3 minutes of an infusion and almost always within the first 10 minutes. Most frequently observed with first or second treatments. Usually prevented by

3- and 24-hour schedules. Premedication regimen, as outlined in Special Considerations, has significantly decreased incidence.	premedication with steroid, overall incidence decreased to less than 3%. When it occurs during drug infusion, treat with hydrocortisone IV, diphenhydramine 50 mg IV, and/or cimetidine 300 mg IV.
3.Neurotoxicity, mainly in the form of sensory neuropathy with numbness and paraesthesia's Dose-dependent effect. Other risk factors include prior exposure to known neurotoxic agents (e.g, cisplatin) and pre-existing medical disorders such as diabetes mellitus and chronic alcoholism More frequent with longer infusions and at doses >175 mg/m Motor and autonomic neuropathy observed at high doses Optic nerve disturbances with scintillating scotomata observed rarely	3.Peripheral neuropathy is less commonly observed with docetaxel than with paclitaxel.
4. Transient asymptomatic sinus bradycardia is most commonly observed cardiotoxicity Occurs in 30% of patients. Other rhythm disturbances are seen, including Mobitz type I Mobitz type II, and third-degree heart block, as well as ventricular arrhythmias	4.Docetaxel may induce contractile dysfunction as a cardiotoxic agent
5.Alopecia. Occurs in nearly all patients, with loss of total body hair	5.Alopecia occurs in up to 80% of patients.
6.Mucositis and/or diarrhea seen in 30%-40% of patients. Mucositis is more common with the 24-hour schedule Mild-to-moderate nausea and vomiting, usually of brief duration	6.Mucositis and/or diarrhea seen in 40% of patients. Mild-to-moderate nausea and vomiting, usually of brief duration.

7.Transient elevations in serum transaminases, bilirubin, and alkaline phosphatase	7.Reversible elevations in serum transaminases, ALPs and bilirubin
8.Onycholysis. Mainly observed in patients receiving >6 courses on the weekly schedule. Not usually seen with the every-3-week schedule[34]	8.Maculopapular skin rash and dry, itchy skin. Most commonly affects forearms and hands. Brown discoloration of fingernails may occur. Observed in up to 50% of patients usually within 1 week after therapy.
9.Anaphylaxis[37]	9.Anaphylaxis[37]
10.swelling at injection site[37]	10.Vesicant, Phlebitis and/or swelling can be seen at the injection site.[34]
11.Genaralised fatigue and asthenia are common, occurring in 60%-70% of patients. Arthralgias and Myalgias are also observed[38]	11.Asthenia[38]

DIFFERENCE BETWEEN PACLITAXEL AND DOCETAXEL

Differences in the drug interaction profiles of docetaxel and paclitaxel are of particular concern when these agents are used in combination with anthracyclines. **While pharmacokinetic interaction between paclitaxel and anthracyclines results in increased levels of the potentially cardiotoxic metabolite doxorubicinol, the absence of any such interaction between conventional doses of docetaxel and anthracyclines means that there is no increased risk for cardiotoxicity with this combination.**[39]

In vitro docetaxel also tends to be more potent in different cell lines and investigational models. While in vitro and in vivo studies suggest that prolonged exposure to paclitaxel is better than a brief exposure, no such tendency is seen for docetaxel, indicating it to be a **schedule-independent drug**.[39] Clinical studies have not confirmed an advantage for prolonged exposure to paclitaxel; but do show differences in the toxicity profiles of the two drugs.[40]With regards to toxicity profiles, neutropenia is the dose-limiting toxicity for both drugs, but differences in non-haematological toxicities are evident. Paclitaxel and docetaxel are the two presently clinically available representatives of the new class of taxane drugs. They share major parts of their structures and mechanisms of action, but differ in several

other aspects. For instance, there is a difference in their tubulin polymer generation, and docetaxel appears twice as active in depolymerization inhibition.[41]

LIMITATIONS OF TAXANES

Solvent-based paclitaxel is associated with multiple side effects including hypersensitivity reactions, peripheral neuropathy, and neutropenia, and therefore has to be administered along with steroid and antihistamine medication.[42]

While highly effective, taxanes also exhibit the typical limitations associated with systemic chemotherapies. First, they are associated with a variety of toxicities including neutropenia, neuropathy, alopecia, hypersensitivity reactions. These toxicities are driven both by the systemic nature of taxanes' mechanisms, as well as some of the excipients used in their formulations. Second, taxanes are administered by IV infusion, which in most cases requires a regular visit to a hospital for a lengthy infusion procedure. Both aspects have significant negative impacts on treatment optimisation and patients' quality of life, which can further exacerbate the challenges of living with advanced cancer.[43]A significant disadvantage of paclitaxel is its high aqueous insolubility and therefore the requirement for ethanol and Cremophor EL as solvents. Solubilization in Cremophor EL results in encapsulation of paclitaxel in drug-trapping micelles, resulting in lower levels of unbound drug and ineffective distribution of the drug to tumour sites.

CHEMOTHERAPY DRUG SEQUENCING IN PACLITAXEL

CISPLATIN

- Paclitaxel should be administered first followed by cisplatin
- Paclitaxel clearance is reduced by approximately 33% when paclitaxel is administered following cisplatin leading to higher toxicity especially myelo-suppression

CARBOPLATIN, PAMIDRONATE.

- Sequencing does not have any impact.
- Paclitaxel should be administered first followed by pamidronate

- Pamidronate can cause nephrotoxicity, which manifests as nephritic syndrome, kidney function deterioration and renal failure, which could alter paclitaxel excretion.

TRASTUZUMAB/PERTUZUMAB

- Administering trastuzumab/pertuzumab first results in better sensitization of breast cancer cells which when followed by paclitaxel causes increased activation and induction of programmed cell death or cell apoptosis.

CYCLOPHOSPHAMIDE/IFOSFAMIDE

- Cyclophosphamide/ifosfamide should be administered first followed by paclitaxel. This lessens cytopenias.

GEMCITABINE

- Paclitaxel followed by gemcitabine causes less risk of hepatotoxicity.

DOXORUBICIN/EPIRUBICIN

- Doxorubicin/epirubicin followed by paclitaxel. Paclitaxel reduces the clearance of doxorubicin leading to increased myelosuppression and mucositis

CHEMOTHERAPEUTIC DRUG SEQUENCING IN DCETAXEL

CISPLATIN

- Docetaxel should be administered first followed by cisplatin for the same reason as paclitaxel.

CARBOPLATIN, PAMIDRONATE

- Sequencing does not have any impact. Docetaxel should be administered first followed by pamidronate for the same reason as paclitaxel

TRASTUZUMAB/PERTUZUMAB

- Administering trastuzumab/pertuzumab first results in better sensitization of breast cancer cells which when followed by docetaxel causes increased activation and induction of programmed cell death or cell apoptosis

CYCLOPHOSPHAMIDE

- Docetaxel should be administered before cyclophosphamide Docetaxel is a cell cycle specific drug, while cyclophosphamide is a cell cycle nonspecific drug, which justifies this infusion sequence. But there are debatable data suggesting reverse sequence purporting less Grade 4 neutropenia.

DOXORUBICIN

- Doxorubicin followed by docetaxel reduces Grade 4 neutropenia

GEMCITABINE

- Sequencing does not have any impact[44]

ADVANTAGES OF DOCETAXEL OVER PACLITAXEL

Differences in the taxoids have been known to exist since early preclinical investigations. In the metastatic setting, docetaxel is the only drug to have shown superiority over single-agent anthracycline therapy as well as combination regimens. At the present time, the choice of taxoid-based regimen should be based on consideration of pharmacokinetics, clinical activity and dosing schedule. Whereas both taxoids are fundamental components of therapy for metastatic breast cancer, the indirect comparison of trials demonstrates that docetaxel is the more clinically effective taxoid. In addition, the differences in the pharmacokinetic profiles of docetaxel and -paclitaxel may explain the simpler treatment schedule and favourable results for docetaxel.

Trials that demonstrate significant differences in survival in the metastatic setting are rare, and the outcomes provide strong support for use of superior agents in the adjuvant setting. Therefore, the superior efficacy of docetaxel compared with paclitaxel that was observed, which was achieved without impacting on patients' quality of life, supports the use of full-

dose docetaxel in the adjuvant setting.[41] In vitro docetaxel also tends to be more potent in different cell lines and investigational models. While in vitro and in vivo studies suggest that prolonged exposure to paclitaxel is better than a brief exposure, no such tendency is seen for docetaxel, indicating it to be a schedule-independent drug.[45]

MECHANISTIC DIFFERENCE BETWEEN PACLITAXEL AND DOCETAXEL.

Table 1.4: Difference in mechanism of action of Paclitaxel and Docetaxel.

Paclitaxel	Docetaxel
Paclitaxel, isolated from the bark of the Pacific yew tree[46]	Docetaxel, synthesized from extracts of the needles of the European yew tree (*Taxus baccata*)[46]
Comparatively less affinity for tubulin binding site.[47]	greater affinity for the tubulin-binding site[47]
Similar microtubule polymerization pattern.[48]	different microtubule polymerization pattern[48]
Short intracellular retention time and lower intracellular concentration in target cells.[49]	Docetaxel is twice as potent as paclitaxel in inhibiting microtubule depolymerisation[49]
Lower thymidine phosphorylase upregulation.[50]	greater thymidine phosphorylase upregulation[50]
Less potent antitumor activity[51]	more potent antitumor activity in in-vitro and in-vivo models[51]
Negligible induction of bcl-2 phosphorylation and apoptosis.[46]	potent induction of bcl-2 phosphorylation and apoptosis[46]
More schedule dependence.[46]	less schedule dependence[46]
Neuropathy more observed.[49]	fluid retention and fatigue more observed.[49]
Cell cycle specificity G_2, M[49]	Cell cycle specificity S, G_2, M[49]

SPECIAL CONSIDERATIONS

All patients should be premedicated prior to TAXOL administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before TAXOL, diphenhydramine (or its

equivalent) 50 mg IV 30 to 60 minutes prior to TAXOL, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before TAXOL.[54]

- IN HEPATIC IMPAIRMENT

For paclitaxel in standard 3 hour in fusion (transaminase and bilirubin) <10*UNL ad ≤1.25*UNL(175mg/m^2). For standard 3 h infusion (transaminase and bilirubin levels) <10 ULN and <1.25 × ULN (175 mg/m^2) <10 ULN and 1.26-2.0 × ULN (135 mg/m^2) <10 ULN and 2.01-5.0 × ULN (90 mg/m^2) >10 ULN or >5.0 x ULN not recommended. In docetaxel Patients with combined abnormalities of ls) transaminases and alkaline phosphatase should not be treated with docetaxel (transaminase and ALP) >2.5 to 5 x ULN and ≤2.5 × ULN, >1.5 to ≤5 × ULN and >2.5 to ≤5 × ULN, reduce by 20% >5 × ULN and/or >5 × ULN Docetaxel should be stopped.

- HYPERSENSITIVITY REACTIONS INSPITE OF APPROPRIATE PREMEDICATIONS

Do not rechallenge in both taxanes.

- IN NEUROPATHY

Dose reduction for all subsequent cycles or discontinue in both taxanes.[55]

NEED FOR THE STUDY

1. Though taxanes are in clinical use for many years to treat different types of cancer, its safety profile and drug interaction details in presence of other drugs are lacking from Indian population.
2. In addition, the prescribing trend of taxanes are also changed due to the introduction of targeted drug therapies. Such data is lacking from Indian population so we planned to conduct this research work.

AIMS AND OBJECTIVES

AIM

To conduct an ambispective observational study to assess the safety profile of Taxanes – Paclitaxel and Docetaxel in cancer patients.

OBJECTIVES

1. To analyze the prescribing pattern of Taxanes
2. To assess safety profile of taxanes
3. To identify drug interactions of taxanes with other drugs if any.
4. To analyze and compare the Adverse effects of Paclitaxel and Docetaxel.