Abbreviations

NSCLC: Non-small cell lung carcinoma

SCLC: small-cell lung carcinoma

RNAi: RNA interference

siRNA: small interfering RNA

RGD: Arginine-Glycine-D-Aspartate

FBS: Fetal boveine serum

MTT: 13-(4, 5-dimethylthiazole-2-yl)-2,5- di-phenyl tetrazolium bromide

DMSO: Dimethyl sulfoxide

DMEM: Dulbecco's Modified Eagle Medium

EDTA: Ethylene Diamine Tetraacetic Acid

EtBr: ethidium bromide

TBE: Tris-Borate-EDTA

CGE: Capillary Gel Electrophoresis

MALDI: Matrix assisted laser desorption ionization

PG: Phosphatidyl Glycerol

Cryo-TEM: Cryo-Transmission Electron Microscopy

RBF: Round bottom Flask

ANOVA: Analysis of Variance

CPE liposomes: Calcium Phosphate Encapsulated Liposomes

PBS: phosphate buffer solution

PDI: Polydispersity Index

PI: propidium iodide

1.1. Introduction

Non-small cell lung cancer (NSCLC) is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. The American Cancer Society's estimates for lung cancer in the United States for 2016 are:(1–4)

About 224,390 new cases of lung cancer (117,920 in men and 106,470 in women)

About158,080 deaths from lung cancer (85,920 in men and 72,160 in women)

Lung cancer is by far the leading cause of cancer death among both men and women; about 1 out of 4 cancer deaths are from lung cancer. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined.(5–7)

Anatomy

NSCLC arises from the epithelial cells of the lung of the central bronchi to terminal alveoli. The histological type of NSCLC correlates with site of origin, reflecting the variation in respiratory tract epithelium of the bronchi to alveoli. Squamous cell carcinoma usually starts near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually originate in peripheral lung tissue.(6,8,9)

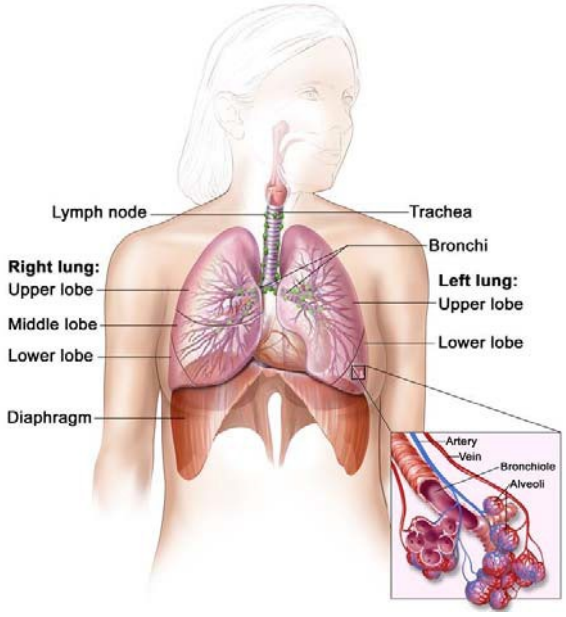

Figure 1.1 Anatomy of the respiratory system.

Non-Small-Cell Lung Cancer(7,10)

Lung cancers can start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli. Lung cancers are thought to start as areas of pre-cancerous changes in the lung. The first changes in the genes (DNA) inside the lung cells may cause the cells to grow faster.(11) Over time, the abnormal cells may acquire other gene changes, which cause them to progress to cancer. As a cancer develops, the cancer cells may make chemicals that cause new blood vessels to form nearby. These blood vessels nourish the cancer cells, which can continue to grow and form a tumor large enough to be seen on imaging tests such as x-rays.(12) At some point, cells from the cancer may break away from the original tumor and spread (metastasize) to other parts of the body. Lung cancer is often a life-threatening disease because it tends to spread in this way even before it can be detected on an imaging test such as a chest x-ray.

Types of lung cancer

There are two major types of lung cancer:

- Small cell lung cancer (SCLC)
- Non-small cell lung cancer (NSCLC)(13,14)

About 85% to 90% of lung cancers are non-small cell lung cancer (NSCLC). There are three main subtypes of NSCLC. The cells in these subtypes differ in size, shape, and chemical make-up when looked at under a microscope. But they are grouped together because the approach to treatment and prognosis (outlook) are often very similar.(6,4)

Squamous cell (epidermoid) carcinoma: About 25% to 30% of all lung cancers are squamous cell carcinomas. These cancers start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the middle of the lungs, near a bronchus.

Adenocarcinoma: About 40% of lung cancers are adenocarcinomas. These cancers start in early versions of the cells that would normally secrete substances such as mucus. This type of lung cancer occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in non-smokers. It is more common in women than in men, and it is more likely to occur in younger people than other types of lung cancer. Adenocarcinoma is usually found in

outer parts of the lung. It tends to grow slower than other types of lung cancer, and is more likely to be found before it has spread outside of the lung.

People with a type of adenocarcinoma called adenocarcinoma in situ (previously called bronchioloalveolar carcinoma) tend to have a better outlook (prognosis) than those with other types of lung cancer.

Large cell (undifferentiated) carcinoma: This type of cancer accounts for about 10% to 15% of lung cancers. It can appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat. A subtype of large cell carcinoma, known as large cell neuroendocrine carcinoma, is a fast-growing cancer that is very similar to small cell lung cancer.

Causes of the Lung Cancer(7,14,15)

Smoking

Tobacco smoking is by far the leading cause of lung cancer. At least 80% of lung cancer deaths are caused by smoking, and many others are caused by exposure to secondhand smoke. Smoking is clearly the strongest risk factor for lung cancer, but it often interacts with other factors. Smokers exposed to other known risk factors such as radon and asbestos are at even higher risk. Not everyone who smokes gets lung cancer, so other factors like genetics likely play a role as well.

Lung cancer in non-smokers

Not all people who get lung cancer are smokers. Many people with lung cancer are former smokers, but many others never smoked at all. Lung cancer in non-smokers can be caused by exposure to radon, secondhand smoke, air pollution, or other factors. Workplace exposures to asbestos, diesel exhaust or certain other chemicals can also cause lung cancers in some people who do not smoke. Lung cancers in non-smokers are often different in some ways from those that occur in smokers. They tend to occur at younger ages. Lung cancers in non-smokers often have certain gene changes that are different from those in tumors from smokers.

Gene changes that may lead to lung cancer

The risk factors for lung cancer can cause certain changes in the DNA of lung cells. These changes can lead to abnormal cell growth and, sometimes, cancer. DNA is the chemical in each

of our cells that makes up our genes – the instructions for how our cells function. We usually look like our parents because they are the source of our DNA.

Some genes contain instructions for controlling when cells grow, divide to make new cells, and die. Genes that help cells grow, divide, or stay alive are called oncogenes. Genes that slow down cell division or cause cells to die at the right time are called tumor suppressor genes.

Inherited gene changes

Some people inherit DNA mutations (changes) from their parents that greatly increase their risk for developing certain cancers. But inherited mutations alone are not thought to cause very many lung cancers. Still, genes do seem to play a role in some families with a history of lung cancer.

Acquired gene changes

Gene changes related to lung cancer are usually acquired during life rather than inherited. Acquired mutations in lung cells often result from exposure to factors in the environment, such as cancer-causing chemicals in tobacco smoke. But some gene changes may just be random events that sometimes happen inside a cell, without having an outside cause.(8)

Treatment Options for Non-Small Cell Lung Cancer(11,16–18)

Surgery provides the best chance of a cure for lung cancer. This is the general approach for stages I and II, and sometimes for stage III and IV. Surgery may be followed by a course of radiation or chemotherapy.(5,14,19–22)

Radiation is used instead of surgery for lung cancer patients who are not as healthy or whose tumors can't be removed surgically. Radiation combined with chemotherapy is generally used to treat Stage III lung cancers.

Chemotherapy alone will not cure lung cancer.(17,20) But used with radiation therapy and surgery, it improves the rates of cure. "Chemo is the icing on the cake when it comes to NSCLC treatment," says Azzoli. When chemotherapy is used in addition to surgery, it is called adjuvant therapy. The goal of adjuvant therapy is to lower the chance of cancer returning. For Stage IV lung cancers, the goal of chemotherapy usually is not to cure the lung cancer, but to relieve symptoms to make the patient more comfortable.(23,24)

Lung Cancer Surgery(10,16,22)

Some or all of the lung, or sections of the lung called lobes, may be removed depending on the size and location of the tumor:

- Segmentectomy or wedge resection removes part of a lobe
- Lobectomy removes an entire lobe
- Pneumonectomy removes an entire lung.

Lung cancer surgery is a serious operation. In most cases, surgeons need to open the rib cage in order to remove the cancer and some surrounding tissue. Most patients spend 5 to 7 days in the hospital after lung cancer surgery, and recovery takes 4 to 8 weeks. A new type of surgery called video-assisted thoracic surgery is less invasive. In this procedure, a small video camera is inserted through a small hole in the chest to help surgeons remove small tumors near the outside of the lung. If you are generally in good health, you should be able to return to normal activities after you recover from lung cancer surgery, even if you had a lung removed. However, if you have a lung disease such as emphysema, you may become short of breath more often after surgery.(13)

If the cancer has spread to another part of your body, or if your cancer recurs, you may have surgery or other procedures to help control it. In people with late stage cancer, surgery may be used to help relieve symptoms and make the patient more comfortable. For example, if a tumor is blocking an airway, laser surgery may be used to make it smaller. In this instance, surgery will not cure the cancer, but can help relieve discomfort or pain. This is called palliative surgery.

Radiation Therapy for Lung Cancer

Radiation therapy can be external or internal. Both use high-energy X-rays or other types of radiation to kill cancer cells or to help keep them from growing. External radiation therapy is delivered from a machine. Internal radiation therapy requires small radioactive “seeds” to be placed in or near a cancerous tumor to help shrink it. Most people with NSCLC receive external radiation therapy. External radiation may be used to treat NSCLC in several ways, depending on the type and stage of the lung cancer.(13)

It can be used in place of surgery for patients who are not healthy enough for surgery or if the tumor can’t be removed by surgery. It may be used with chemotherapy to treat Stage III cancers. Chemotherapy and radiation therapy may be given at the same time.

It can also be used as palliative therapy in late stage cancer to lessen symptoms and relieve pain. External beam radiation therapy will not make you radioactive. However, some healthy tissue may be harmed along with cancer cells during treatment, so you may notice some side effects. These include:

- Sunburn-like redness on the skin where the radiation is focused
- Irritation of the esophagus
- Fatigue

A new form of radiation therapy, called stereotactic body radiation (SBRT), is becoming widely used in patients with early stage cancer who are not able to have surgery. This treatment uses highly targeted, high-dose radiation that kills cancer cells while sparing normal tissue. "SBRT is a more precise therapy, and it has few side effects.

Chemotherapy for Lung Cancer(13,25)

Chemotherapy uses drugs to kill cancer cells. Usually given by injection, the drugs travel throughout the body in the bloodstream, so chemo is useful for metastasized cancers. "In the last 6 or 7 years, there has been a revolution in how chemotherapy is used for treatment of NSCLC." "In 2003, studies first reported the benefits of using chemotherapy as adjuvant therapy. Prior to that, chemotherapy was not routinely given to patients with stage I or stage II cancer. Now medical oncologists see more early stage lung cancer patients. We discovered that by adding chemotherapy to surgery or to radiation treatment at earlier stages, more patients can be cured." Depending upon a person's health, the stage of lung cancer, and the type of cancer, chemotherapy may be used in several ways:

- After surgery as adjuvant therapy to help kill any remaining cancer cells
- Before surgery to control the disease prior to surgery. This is called neoadjuvant therapy.
- With radiation therapy, either one after another or at the same time. Chemotherapy given simultaneously with radiation therapy is called chemoradiation.
- As a single therapy

Chemotherapy treatment should begin within two months after lung cancer surgery. The decision about which chemotherapy drugs to use is based on a number of factors. Usually, two chemo drugs are used together. This is called combination chemotherapy. For people in poor health, only one drug may be used. (11,16,24)

Chemotherapy works by killing rapidly growing cancer cells. But the drugs can't tell the difference between cancer cells and other cells in the body that also divides quickly. These types of cells occur in hair follicles, bone marrow, and the lining of the intestines and mouth. As a result, these healthy cells may become damaged, leading to side effects such as:

- Loss of appetite
- Nausea
- Fatigue
- Increased risk of infection

Advances in chemotherapy drugs and in the drugs used to treat side effects have eliminated certain side effects for people receiving chemotherapy for NSCLC. In many cases, you won't lose your hair.(23,26)

Targeted Cancer Therapy(16–18,27–31)

As noted above, most current anticancer agents do not greatly differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. Consequently, systemic applications of these drugs often cause severe side effects in other tissues (such as bone marrow suppression, cardiomyopathy, and neurotoxicity), which greatly limits the maximal allowable dose of the drug. In addition, rapid elimination and widespread distribution into nontargeted organs and tissues require the administration of a drug in large quantities, which is not economical and often complicated owing to nonspecific toxicity.(28,32)

Nanotechnology offers a more targeted approach and could thus provide significant benefits to cancer patients. In fact, the use of nanoparticles for drug delivery and targeting is likely one of the most exciting and clinically important applications of cancer nanotechnology.(27,33–38)

Passive Targeting(39,40,32)

Rapid vascularization in fast-growing cancerous tissues is known to result in leaky, defective architecture and impaired lymphatic drainage. This structure allows an EPR effect, resulting in the accumulation of nanoparticles at the tumor site. For such a passive targeting mechanism to work, the size and surface properties of drug delivery nanoparticles must be controlled to avoid uptake by the reticuloendothelial system (RES). To maximize circulation times and targeting ability, the optimal size should be less than 100 nm in diameter and the surface should be

hydrophilic to circumvent clearance by macrophages. A hydrophilic surface of the nanoparticles safeguards against plasma protein adsorption and can be achieved through hydrophilic polymer coatings such as PEG, poloxamines, poloxamers, polysaccharides, or through the use of branched or block amphiphilic copolymers.

Active Targeting(11,28,40,32,41–45)

Active targeting is usually achieved by conjugating to the nanoparticle a targeting component that provides preferential accumulation of nanoparticles in the tumor bearing organ, in the tumor itself, individual cancer cells, or intracellular organelles inside cancer cells. This approach is based on specific interactions, such as lectin carbohydrate, ligand-receptor, and antibody-antigen. Nanoparticle drug delivery and targeting using receptor-mediated endocytosis.(46,47) The nanoparticle drug is internalized by tumor cells through ligand-receptor interaction. Depending on the design of the cleavable bond, the drug will be released intracellularly on exposure to lysosomal enzymes or lower pH.(36,48)

Over-expression of EGFR has been associated with angiogenesis and poor prognosis in NSCLC. Cetuximab is a chimeric mAb that targets the EGFR pathway by binding to the extracellular domain of the receptor and in this way inhibiting the receptor-associated tyrosine kinase (TK) activity. Furthermore, inhibitors of TK activity of EGFR have been used for targeting the receptor pathway. Small molecule, such as erlotinib and gefitinib, compete reversibly with ATP to bind to the intracellular catalytic domain of EGFR TK and, thus, inhibit EGFR autophosphorylation and downstream signaling.(28)(49,50)

Nanoparticle Drugs(43,51–53)

Nanotechnology is beginning to change the scale and methods of drug delivery (Figure 1.2). Therapeutic and diagnostic agents can be encapsulated, covalently attached, or adsorbed onto nanoparticles. These approaches can easily overcome drug solubility issues, which has significant implications because more than 40% of active substances being identified through combinatorial screening programs are poorly soluble in water. Conventional and most current formulations of such drugs are frequently plagued with problems such as poor and inconsistent bioavailability.(11,54,46)

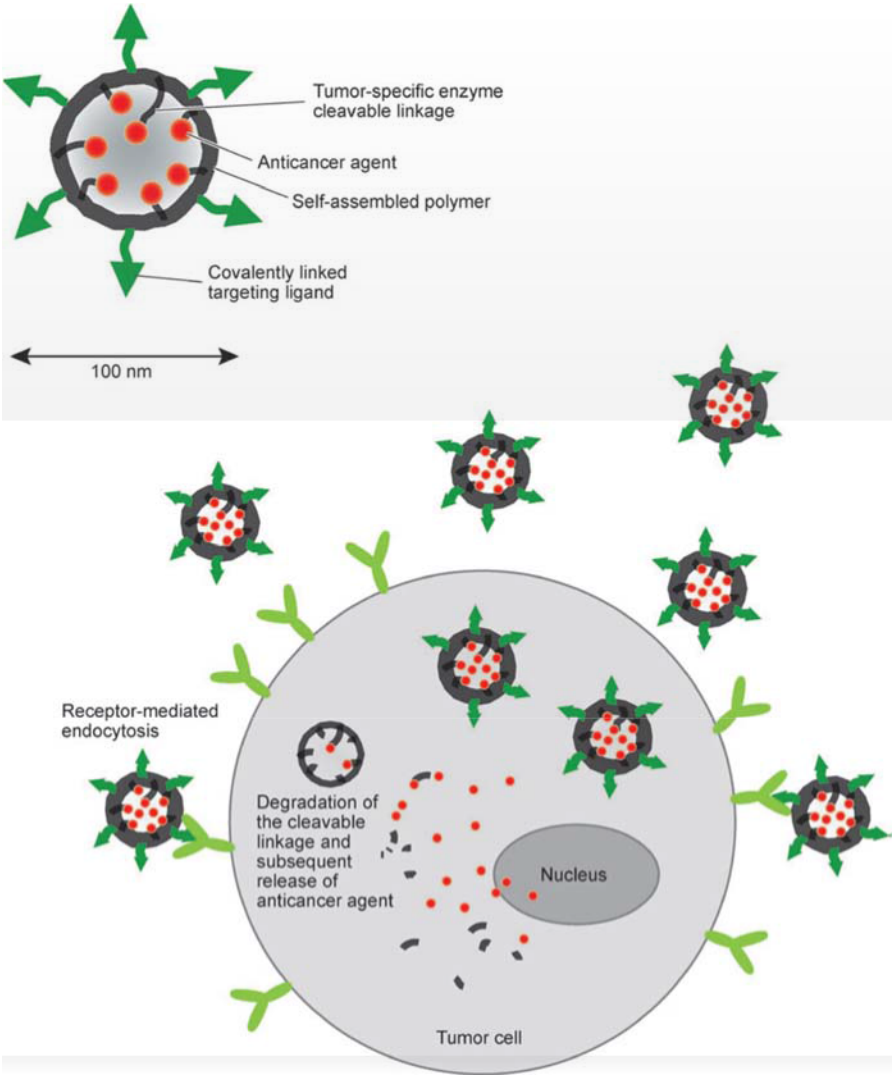

Figure 1.2 Delivery of the nanoparticle drugs by receptor-mediated endocytosis and controlled drug release inside the cytoplasm.

For decades, researchers have been developing new anticancer agents and new formulations for delivering chemotherapy drugs. Docetaxel is one of the most widely used anticancer drugs in the clinic. It is a microtubule-stabilizing agent that promotes tubulin polymerization, disrupting cell division and leading to cell death. It displays neoplastic activity against primary epithelial ovarian carcinoma and breast, colon, and lung cancers. Because it is poorly soluble in aqueous solution, the formulation available currently is Chremophor EL and Ethanol.(55–57)

1.2. Objective of the Proposed Work

The objective of the proposed investigation was to develop nanoparticles of docetaxel and active targeting with Cetuximab mAb to EGFR over expressed cell.

1.3. Rationale

To improve efficacy, safety and reduce the toxicity of docetaxel drug by directly targeting cancerous cell using EGFR receptor specific conjugation approach to achieve specific targeting. The current cure chemotherapy for lung cancer has limitation being non-selective and manifests in dose related toxicity.

1.4. Hypothesis

It is hypothesized that conjugation of receptor specific antibody cetuximab to docetaxel-encapsulated nanoparticles will enhance the localization effect of the anticancer drugs and thereby minimizing drug related peripheral side effects.

1.5. Research Design and Method

1. Development and characterization of Docetaxel-encapsulated nanoparticles
2. Development and characterization of Cetuximab conjugated Docetaxel nanoparticles
3. Selectivity and efficacy of Cetuximab conjugated Docetaxel nanoparticles using in-vitro cell line studies and In-vivo model

1.6. Expected Results

The scientific literature refers to the enhanced selectivity and cytotoxic effects of anticancer agents with a ligand attachment like antibodies. The exposure of the tumor cells selective to antibody may show anticancer effects at lower doses of the drug with antibody conjuageted nanoparticles.

1.7. Work Plan

1. Development and Characterization of Docetaxel-encapsulated nanoparticles.
2. Development and Characterization of Cetuximab conjugated Docetaxel nanoparticles.
3. Cell line studies, including intracellular uptake studies, cytotoxicity study, cell cycle analysis in lung cancer cell lines.
4. Tumor suppression studies to assess the safety profile of developed Cetuximab conjugated Docetaxel nanoparticles.
5. Stability studies of developed formulations at storage and accelerated conditions.

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2.1. Lung Cancer

The lungs are located in the chest. They help you breathe. When you breathe, air goes through your nose, down your windpipe (trachea), and into the lungs, where it spreads through tubes called bronchi. Most lung cancer begins in the cells that line these tubes.(1)

There are two main types of lung cancer:

I Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.(2)

I Small cell lung cancer makes up about 20% of all lung cancer cases.(3)

If the lung cancer is made up of both types, it is called mixed small cell/large cell cancer. If the cancer started somewhere else in the body and spread to the lungs, it is called metastatic cancer to the lung.(4)

2.1.4. Prevention and Treatment

Eliminating tobacco smoking is a primary goal in the prevention of lung cancer, and smoking cessation is an important preventive tool in this process.

- **Surgery**: Positron emission tomography (PET)(1,2) is used to determine whether the disease is localized and amenable to surgery or whether it has spread to the point where it cannot be cured surgically. Video-assisted thoracoscopic surgery (VATS) and VATS lobectomy have allowed for minimally invasive approaches to lung cancer surgery that may have the advantages of a quicker recovery.(1,5)
- **Radiotherapy**: Radiotherapy is often given together with chemotherapy, and may be used with curative intent in patients with non-small-cell lung carcinoma who are not eligible for surgery. This form of high intensity radiotherapy is called radical radiotherapy. A refinement of this technique is continuous hyperfractionated accelerated radiotherapy (CHART), in which a high dose of radiotherapy is given in a short time period. For small-cell lung carcinoma cases that are potentially curable, chest radiation is often recommended in addition to chemotherapy.(6,7) The use of adjuvant thoracic radiotherapy following curative intent surgery for non-small-cell lung carcinoma is not well established and is controversial. Benefits, if any, may only be limited to those in whom the tumor has spread to themediastinal lymph nodes.(1,4,5,8) For both non-small-cell lung carcinoma and small-cell lung carcinoma patients, smaller doses of radiation to the chest may be used for symptom control(palliative radiotherapy. Brachy therapy

(localized radiotherapy) may be given directly inside the airway when cancer affects a short section of bronchus. It is used when inoperable lung cancer causes blockage of a large airway. Patients with limited-stage small-cell lung carcinoma are usually given prophylactic cranial irradiation (PCI).(3) This is a type of radiotherapy to the brain, used to reduce the risk of metastasis. More recently, PCI has also been shown to be beneficial in those with extensive small-cell lung cancer. In patients whose cancer has improved following a course of chemotherapy, PCI has been shown to reduce the cumulative risk of brain metastases within one year from 40.4% to 14.6%. Recent improvements in targeting and imaging have led to the development of extracranial stereotactic radiation in the treatment of early-stage lung cancer. In this form of radiation therapy, very high doses are delivered in a small number of sessions using stereotactic targeting techniques. Its use is primarily in patients who are not surgical candidates due to medical comorbidities.(5,9,10)

- **Chemotherapy**: The chemotherapy regimen depends on the tumor type.
  - **Small-cell lung carcinoma**: Even if relatively early stage, small-cell lung carcinoma is treated primarily with chemotherapy and radiation. In small-cell lung carcinoma, cisplatin and etoposide are most commonly used. Combinations with carboplatin, gemcitabine, paclitaxel, vinorelbine, topotecan, and irinotecan are also used.(11)
  - **Non-small-cell lung carcinoma**: Primary chemotherapy is also given in advanced and metastatic non-small-cell lung carcinoma. Testing for the molecular genetic subtype of nonsmall-cell lung cancer may be of assistance in selecting the most appropriate initial therapy.For example, mutation of the epidermal growth factor receptor gene may predict whether initial treatment with a specific inhibitor or with chemotherapy is more advantageous. Advanced non-small-cell lung carcinoma is often treated with cisplatin or carboplatin, in combination with gemcitabine, paclitaxel, docetaxel, etoposide, or vinorelbine. Bevacizumab improves results in non-squamous cancers treated with paclitaxel and carboplatin in patients less than 70 years old who have a reasonable general performance status. Pemetrexed has been studied extensively in non-small-cell lung cancer, with numerous studies since 1995.(7,12) For adenocarcinoma and large-cell lung cancer, cisplatin with

pemetrexed was more beneficial than cisplatin and gemcitabine; squamous cancer had the opposite results. As a consequence,sub typing of non-small lung cancer histology has become more important.(13,6,14–16) Bronchoalveolar carcinoma is a subtype of non-small-cell lung carcinoma that may respond to gefitinib and erlotinib.

- **Maintenance therapy**: In advanced non-small-cell lung cancer there are several approaches for continuing treatment after an initial response to therapy. Switch maintenance changes to different medications than the initial therapy and can use pemetrexed, erlotinib, and docetaxel, although pemetrexed is only used in non-squamous NSCLC.(6,15)
- **Adjuvant chemotherapy**: Adjuvant chemotherapy refers to the use of chemotherapy after apparently curative surgery to improve the outcome. In non-small-cell lung cancer, samples are taken during surgery of nearby lymph nodes. If these samples contain cancer, the patient has stage II or III disease. In this situation, adjuvant chemotherapy may improve survival by up to 15%. Standard practice has often been to offer platinum-based chemotherapy (including either cisplatin or carboplatin). However, the benefit of platinum-based adjuvant chemotherapy was confined to patients who had tumors with low ERCC1 (excision repair cross-complementing 1) activity.(1,5,12,17) Adjuvant chemotherapy for patients with stage IB cancer is controversial, as clinical trials have not clearly demonstrated a survival benefit. Trials of preoperative chemotherapy (neoadjuvant chemotherapy) in resectable non-small-cell lung carcinoma have been inconclusive.

2.2. Drug Profile

Docetaxel is a clinically well established anti-mitotic chemotherapy medication used mainly for the treatment of breast, ovarian, and non-small cell lung cancer.(14) Docetaxel binds to microtubules reversibly with high affinity and has a maximum stoichiometry of one mole docetaxel per mole tubulin in microtubules.

Indication

For the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. Also used as a single agent in the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.(16)

2.2.1. Mechanism of Action

Docetaxel interferes with the normal function of microtubule growth. Whereas drugs like colchicine cause the depolymerization of microtubules in vivo, docetaxel arrests their function by having the opposite effect; it hyper-stabilizes their structure. This destroys the cell's ability to use its cytoskeleton in a flexible manner. Specifically, docetaxel binds to the β-subunit of tubulin. Tubulin is the "building block" of mictotubules, and the binding of docetaxel locks these building blocks in place. The resulting microtubule/docetaxel complex does not have the ability to disassemble. This adversely affects cell function because the shortening and lengthening of microtubules (termed dynamic instability) is necessary for their function as a transportation highway for the cell. Chromosomes, for example, rely upon this property of microtubules during mitosis. Further research has indicated that docetaxel induces programmed cell death (apoptosis) in cancer cells by binding to an apoptosis stopping protein called Bcl-2 (B-cell leukemia 2) and thus arresting its function.(18)

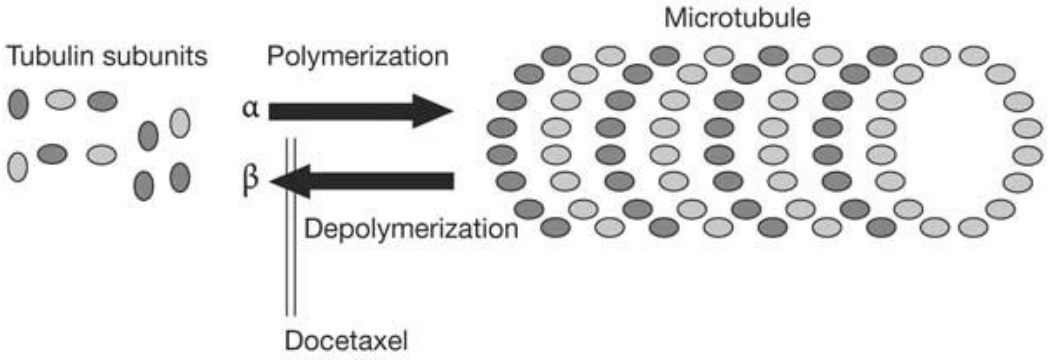

Figure 2.1 Mechanism of Action of Docetaxel

2.2.2. Absorption, Fate, and Elimination(19)

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 5 to 115 mg/m^2 in phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three compartment pharmacokinetic model with half-lives for the alpha, beta and gamma phases of 4 minutes, 36 minutes and 11.1 hours, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100 mg/m^2 dose given as a one hour infusion, a mean peak plasma level of 3.7 microgram/mL was obtained with a corresponding area under the curve (AUC) of 4.6 hours.microgram/mL. Mean values for total body clearance and steady-state volume of distribution were 21 L/hour/m^2 and 113 L, respectively.(20)

A study of 14C-docetaxel has been conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group; within seven days, the urinary and fecal excretion account for about 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity (60% of the administered dose) recovered in feces is excreted during the first 48 hours as one major and three minor inactive metabolites and very low amounts of unchanged drug.

A population pharmacokinetic analysis has been performed with docetaxel in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not altered by the age or sex of the patient. In a small number of patients (n = 23) with clinical chemistry data suggestive of mild to moderate liver function impairment (ALT, AST greater than or equal to 1.5 times the upper limit of normal, associated with alkaline phosphatase greater than or equal to 2.5 times the upper limit of normal), total clearance was lowered by, on average, 27% (see Dosage and Administration). Docetaxel clearance was not modified in patients with mild to moderate fluid retention. No data are available in patients with severe fluid retention.

Docetaxel is more than 95% bound to plasma proteins. Dexamethasone did not affect protein binding of docetaxel. The effect of prednisone on the pharmacokinetics of docetaxel administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetics of docetaxel was observed.

Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of docetaxel and the effect of docetaxel on the pharmacokinetics of capecitabine showed no effect of capecitabine on the pharmacokinetics of docetaxel (Cmax and AUC) and no effect of docetaxel on the pharmacokinetics of the main capecitabine metabolite 5'DFUR.

The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual medicine.

2.2.3. Therapeutic Uses

For treatment after failure of prior platinum-based chemotherapy, TAXOTERE was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials.(16,19,21)

2.2.4. Clinical Toxicities

Oral LD50 in rat is >2000 mg/kg. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.(19,20)

Table 2.1 Drug Profile(22,23)

Name	Docetaxel
Chemical mane(IUPAC)	1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}
Proprietary name	Taxotere
Molecular formula	C43H53NO14
Molecular weight	807.8792
Physicochemical properties	
Physical state and Appearance	White to off white color powder
Melting point	232 °C
Log P	2.4
pka value	pKa (strongest acidic): 10.96

	pKa (strongest basic): -3
Solubility	Soluble in DMSO at 200 mg/mL; soluble in ethanol at 100 mg/mL; very poorly soluble in water
Half life	Dose-dependent. Doses of 70 mg per square meter of body surface area (mg/m^2) or higher produce a triphasic elimination profile. With lower doses, assay limitations precluded detection of the terminal elimination phase. The half-life of the alpha, beta, and gamma phase are 4 minutes, 36 minutes, and 11.1 hours, respectively.
Dose	20mg/mL
Structure