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SAFETY AND ANTITUMOR ACTIVITY OF GEFITINIB: AN OVERVIEW

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Keywords:

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ABSTRACT: Gefitinib is an epidermal growth factor receptor tyrosine kinase inhibitor, a promising anticancer agent for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), especially in EGFR mutated patients. It acts by interfering with the proliferation and survival of cancer cells and other host-dependent process promoting cancer cell growth by blocking signal transduction pathways. The major advantage of Gefitinib over standard chemotherapy is that it selectively inhibits cellular pathways involved in tumor survival with minimal effect on normal cells. Gefitinib was the first agent to be tested in clinical trials among tyrosine kinase inhibitors class of anticancer drugs. Gefitinib is a very slightly soluble novel anticancer drug whose solubility and dissolution can be improved by its complexation with cyclodextrins. Gefitinib is a generally well-tolerated treatment, with skin rash and diarrhea being the most common treatment adverse effects. Gefitinib has the potential of stimulating cell immunity against malignant cells. Binding of Gefitinib to human plasma protein is extensive. This article reviews the safety and efficacy of Gefitinib along with chemistry, mechanism, pharmacokinetics, drug interactions and special precautions to be taken in special cases like Geriatrics, Paediatrics, Pregnant women and nursing women during treatment with Gefitinib.

INTRODUCTION: Gefitinib is an anticancer drug classified under the category of tyrosine kinase inhibitors [1]. It interferes with the growth and spread of new cancer cells. Gefitinib acts as an antitumor medicine relatively a cytotoxic drug [2]. A chemical Tyrosine kinase is responsible for provoking the growth of cancer cells. Gefitinib is an innovative EGFR tyrosine kinase inhibitor which binds to the enzyme ATP binding site and is competitive with ATP and noncompetitive with peptide substrates [3].

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Gefitinib has been found to have antitumor activity in those patients who have become resistant to other anticancer drugs [4]. The epidermal growth factor receptor (EGFR) is one transmembrane receptor tyrosine kinase of the human epidermal growth factor receptor (HER) family, has an important role in the proliferation and metastasis of cancer cells. It is frequently overexpressed in common solid tumors and has become a favored target for orally administered small molecule and antibody-based therapy [5].

The orally administered EGFR inhibitor Gefitinib was considered as third-line therapy for non-small-cell lung cancer and was approved by the Food and Drug Administration for treatment of cancer in May 2003 [6]. It was found in studies during phase I clinical trials that Gefitinib was active against non-small-cell lung cancer across a broad range of

doses and studies during phase II clinical trials showed that response rate obtained was found in between 9% to 19% with the doses of 250 or 500 mg per day [7-8]. Gefitinib is an epidermal growth factor receptor inhibitor for Tyr992, Tyr1173, Tyr992 and Tyr1173 in the NR6W and NR6wtEGFR cells with IC_{50} of 37 nM, 37nM, 57 nM and 26 nM respectively [9].

The non-small cell lung cancer (NSCLC) is the leading cause of death from cancer. Chemotherapy based on Platinum and combinations of platinum with Gemcitabine and Paclitaxel reproduced more improvement in survival. The patients in whom first-line chemotherapy was unsuccessful, second-line chemotherapy with Docetaxel was approved, but the response reported was only 5-10% [10]. EGFR is overexpressed, or deregulated in many human solid tumors, including breast, ovarian, non–small-cell lung cancer, colorectal, head and neck cancers. This activation leads to enhancement in the growth of tumor *via* increasing cell proliferation, motility, adhesion, invasive capacity, and by blocking apoptosis.

It is reported that deregulation and overexpression of EGFR are believed to be coupled based on poorer diagnosis in patients and are linked with metastasis, late-stage disease, resistance to chemotherapy, hormonal therapy, and radiotherapy [11-14]. Recently, several studies were carried out to elucidate the efficacy of Gefitinib monotherapy as first-line treatment for NSCLC [15-18]. It was found that Gefitinib was effective in the reduction of the tumor mass and improvement of quality of life and more favorable tolerability profile compared with Carboplatin and Paclitaxel chemotherapy as first-line treatment in Asian patients who were chemo-naive with NSCLC [19].

The epidermal growth factor receptor (EGFR) corresponds to a subdivision of four closely related receptors: EGFR (ErbB-1), HER2/*neu* (ErbB-2), HER3 (ErbB-3), and HER4 (ErbB-4) [20]. The inhibition of in vitro EGFR activity, inhibition of EGF-stimulated tumor cell growth and blockage of autophosphorylation stimulated by EGF in tumor cells are the main functions of Gefitinib. Gefitinib restricts the EGF-stimulated growth of human umbilical vein endothelial cells in comparison with FGF- or VEGF-stimulated growth. It has been found that Gefitinib is much more selective for EGFR than HER2. There is a major role of Gefitinib in inhibition of growth and phosphorylation of HER2 in numerous HER2-overexpressing cell lines [21-22]. The EGFR is a 170-kd plasma membrane glycoprotein composing an extracellular ligand-binding domain and an intracellular protein (tyrosine) kinase domain. Extracellular ligand-binding domain is a transmembrane lipophilic segment, and an intracellular protein (tyrosine) kinase (TK) domain has a regulatory carboxyl-terminal segment [23-24].

Activation of EGFR can also be done via a ligand-independent mechanism. This activation of EGFR TK has been evidenced as a chief initiating event that generates a flood of intracellular signaling events regulating cell proliferation, differentiation, survival, angiogenesis, and metastasis, all processes that are acute to cancer progression [25].

Chemistry: Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, *N*-(3-chloro- 4- fluorophenyl)- 7- methoxy- 6- [3- 4-morpholin) propoxy], and the molecular structure has been illustrated in **Fig. 1**.

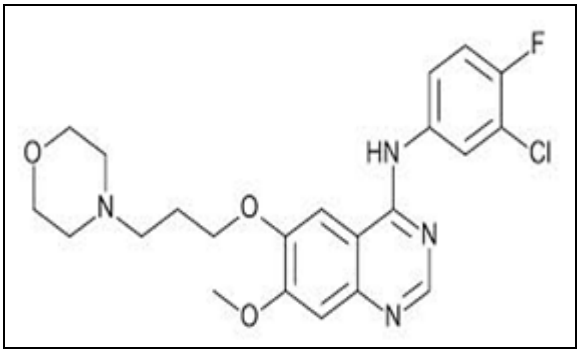

FIG. 1: MOLECULAR STRUCTURE OF GEFITINIB

It has the molecular formula $C_{22}H_{24}ClFN_4O_3$ with the molecular mass of 446.9 and is a white colored powder/brown-colored powder. Gefitinib is a free base and has pK_a of 5.4 and 7.2 and accordingly ionizes constantly in solution as there is a decline in pH. Gefitinib is sparingly soluble at pH 1, insoluble above pH 7, with the solubility falls acutely between pH 4-6. Among nonaqueous solvents, Gefitinib is freely soluble in dimethylsulphoxide and glacial acetic acid, soluble in pyridine, sparingly soluble in tetrahydrofuran, slightly soluble in methanol, ethanol (99.5%), acetonitrile, ethyl acetate and propan-2-ol [26].

Mechanism of Action: Gefitinib inhibits a protein known as epidermal growth factor receptor (EGFR) which helps in the growth and spread of cancer cells [28]. EGFRs are structures on the surface of cancer cells. The receptors allow the epidermal growth factor, which is a protein present in the body to attach to them. When the receptors get attached to the epidermal growth factor (EGF), it results in an enzyme known as tyrosine kinase (TK) to activate chemical processes inside the cell which make cell to grow and divide [29]. Gefitinib gets attached to the EGF receptor on the cell, and the receptor activation is prevented, resulting in the inhibition of the division and growth of cancer cells [30].

Gefitinib belongs to the first selective inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain. The target protein epidermal growth factor receptor includes HER 1(erb-B1), HER 2(erb-B2), and HER 3(erb-B3) receptors. Overexpression of EGFR has been seen in the cells of certain types of human carcinomas as in lung and breast cancers. It results in inappropriate activation of an intracellular signal transduction cascade that involves the Ras protein and inhibits apoptosis (anti-apoptotic Ras signaling cascade), ultimately leading to uncontrolled proliferation of the cell.

A mutation in EGFR tyrosine kinase domain results in activation of anti-apoptotic pathways in case of non-small cell lung cancers which are sensitive to Gefitinib [31-32]. These mutations are responsible for increased sensitivity to tyrosine kinase inhibitors such as Gefitinib. These mutations are mostly seen in Asians, women, and non-smokers [33].

Gefitinib works by inhibition of EGFR tyrosine kinase via binding to the adenosine triphosphate (ATP)-binding site of the enzyme. So the activation of the anti-apoptotic Ras signal transduction cascade is inhibited, which is the function of the EGFR tyrosine kinase. The phosphorylation of several tyrosine kinases inside the cells is inhibited by Gefitinib, although Gefitinib has a role in antitumor effect in the association of tyrosine kinase with the epidermal growth factor receptor. Epidermal growth factor receptor constitutes on normal and cancer cells, but its presence on cancer cells results in the antitumor effect of Gefitinib [34].

Gefitinib inhibits all tyrosine phosphorylation sites on EGFR expressing cell lines. Tyr1173 and Tyr992 are less sensitive phosphorylation sites which require higher concentrations of Gefitinib for inhibition. If EGFRvIII-expressing cells are exposed to low concentrations of gefitinib (0.01–0.1μM) for a long time, EGFRvIII dimerization gets induced leading to increased phosphotyrosine load of the receptor, increased signaling to ERK and stimulation of proliferation and anchorage-independent growth. On the other hand, higher concentrations of gefitinib (1–2 μM) significantly lowered EGFRvIII phosphotyrosine load, EGFRvIII-mediated proliferation, and anchorage-independent growth. If the dose of Gefitinib ranges between 0.1 to 0.5μM, it significantly facilitates the colony formation in cell lines. However, Gefitinib in the concentration of 2 μM causes complete blockage of colony formation. Gefitinib inhibits the phosphorylation of EGFR and ERK briskly and uniformly after stimulation of EGF in both the high- and low-EGFR-expressing cell lines upto72 h [35].

Pharmacokinetics: Daily administration of Gefitinib tablet orally to cancer patients resulted in double accumulation in comparison to single dose administration. Steady-state plasma concentrations are achieved within 10 days. After oral administration, Gefitinib is slowly absorbed with a mean bioavailability of 60%. Elimination is by metabolism (primarily CYP3A4) and excretion in feces. The elimination half-life is about 48 h [37-38]. Pharmacokinetics of Gefitinib has been illustrated in **Table 1**.

Absorption and Distribution: On oral administration of Gefitinib to cancer patients, peak plasma levels are attained within 3-7 hr. The absolute bioavailability of Gefitinib was found to be 60%. Bioavailability is not significantly altered by food. With the improvement in the solubility and dissolution property, the bioavailability of drug can be increased. Different modes can be employed to improve it, including solvent dispersion on an inert carrier, micronization of drug particles, nanoparticle formation, hot-melt extrusion, and cyclodextrin complexation. It was found through the liquid and solid state complexation studies that Gefitinib can form a stable inclusion complex with the three

Cyclodextrins named as β-cyclodextrin, hydroxy-propyl-β-cyclodextrin and randomly methylated-β-cyclodextrin. Hydroxypropyl-β-cyclodextrin showed the greatest improvement in the dissolution of Gefitinib followed by randomly methylated-β-cyclodextrin and β-cyclodextrin, with further improvement upon the addition of PVP or HPMC. The dissolution of Gefitinib from the CD complexes was markedly enhanced by the addition of hydrophilic polymers. The Gefitinib-HP β-CD (1:1) complex yielded 50% dissolution in 1 h whereas the addition of 10% and 25% w/w PVP increased the dissolution to 80% and 90%, respectively. Similarly, the addition of HPMC at 10% w/w and 25% w/w to the complex increased the dissolution of the complex to 85% and 95%, respectively in 1 h [27].

TABLE 1: PHARMACOKINETICS OF GEFITINIB

Pharmacokinetics	Observations
Oral Absorption [39]	60% bioavailability on oral absorption is 60% which is reduced by 47% at gastric pH >5 Not significantly altered by food Time to peak plasma concentration: 3 – 7 h
Distribution [40-43]	Extensively distributed The volume of distribution: 1400 – 1600 L Plasma protein binding is not concentration dependent; 90% with serum albumin and α_1-acid glycoprotein
Metabolism [44-48]	Extensive hepatic metabolism *via* CYP3A4 O-desmethyl Gefitinib is the active metabolite of Gefitinib with 1/14th potency. Inactive metabolite(s) are also produced
Excretion [49-51]	Clearance: 500 mL/min, Terminal half life : 30.5 – 41 h Urinary excretion: <4% , Faecal excretion : 86%

A high-fat breakfast increased exposure to Gefitinib. Gefitinib exhibits linear kinetics over the therapeutic dosing range. On regular oral dose, within 10 days, steady-state plasma levels were achieved [39]. After intravenous administration, Gefitinib is extensively distributed throughout the body with a mean steady-state volume of distribution of 1400 L. Protein binding is 90% primarily to serum albumin and alpha 1-acid glycoprotein [40-41]. A large distribution of the drug in tissues such as liver, kidney, gastrointestinal tract, lung, and tumors is due to the very high distribution volume of Gefitinib. The accumulation property in the lungs was 10 times higher in comparison to plasma [42-43].

Metabolism and Elimination: Gefitinib undergoes extensive hepatic metabolism in humans, predominantly by CYP3A4. Three sites have been identified for biotransformation of Gefitinib including the metabolism of the N-propoxymorpholino-group, demethylation of the methoxy-substituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group. *In-vitro* and *in-vivo* studies indicated that Gefitinib is mainly metabolized by cytochrome P450-dependent (CYP) activities, including CYP3A4, CYP3A5, and CYP2D6 in the liver [44-46]. The main metabolic pathway characterized by using human liver microsomes includes morpholine ring opening, O-demethylation of the methoxy-substituent on the quinazoline ring structure and oxidative defluorination of the halogenated phenyl group [47-48].

Elimination is by metabolism (predominantly CYP3A4) and excretion in feces. Renal elimination of drug and metabolites is less than 4% of the administered dose. Excretion via the feces is predominantly 86%; the terminal half-life is 30.5 - 41 h. The prime organ for clearance of Gefitinib is liver; with total plasma clearance value is 595 mL/min [49-50].

Toxicity Studies: According to clinical studies, acute toxicity upon oral administration of Gefitinib up to 500mg has been low. In non-clinical studies, a single dose about 80 times the recommended clinical dose on an mg/m^2 basis that of 12,000 mg /m^2 was found lethal to rats. Half of this dose caused no mortality in mice. Overdose symptoms include diarrhea and skin rash [52].

Precautions in Special Population: Gefitinib is recommended for the first line treatment of patients suffering from locally progressed or metastasized non-small cell lung cancer with EGFR activating mutations.

Geriatrics: In patients with age either equal to or greater than 65 years, no differences in safety or efficacy were observed between younger and older patients [81].

Pediatrics: Gefitinib is not recommended for use in pediatric patients, as safety and effectiveness of Gefitinib treatment in pediatric patients has not yet been substantiated. In phase I & II clinical trial of Gefitinib and radiation therapy among cancer patients of age equal to or less than 16 years, CNS hemorrhages were observed in 4 patients out of 45 patients [61]. Trial of Gefitinib alone in a child suffering from ependymoma also resulted in CNS hemorrhage. [51].

Pregnancy: Female fertility has been reported to decrease at a dose of 20 mg/kg/day. The number of offsprings born alive was reduced in pregnant women treated with 5 mg/kg/day till weaning starting from organogenesis. High neonatal mortality was reported in pregnant rats treated with 20 mg/kg/day [51].

Lactating Mothers: Concentrations of Gefitinib and its metabolites were reported to be 11-19 times higher in milk than in blood after administering carbon-14 labeled Gefitinib at a dose of 5 mg/kg to rats 14 days postpartum orally. These data suggest that usage of Gefitinib should be avoided in breastfeeding patients [52].

Therapeutic Uses: Gefitinib is one of the first agents for the treatment of non-small cell lung cancer in its antineoplastic class to be tested in clinical trials which have given various promising results. In breast cancer and in cancers where over-expression of epidermal growth factor receptor is involved, Gefitinib can be prescribed. Gefitinib is under analysis in phase I study in patients with different solid tumors and phase II study for malignant mesothelioma [53].

Gefitinib has the Potential to Stimulate Cell Immunity against Malignant Cells: It has been reported that Gefitinib activates platelets and RANTES (Regulated on Activation, Normal T-cells Expressed and Secreted) is released from the activated platelets, and chemokine secretion by monocytes in the inflammatory lesion is regulated by the activated platelets [54]. Lymphocyte migration is commenced at the focal tissue, and monocytes are also activated, resulting in several immune responses to tumor cells at the focal tissue. The clinical efficacy of Gefitinib therapy may be brought by the reduction in the angiogenesis *via* blockade of EGFR and thus causing tumor necrosis. Cell immunity against the tumor is raised due to the activation of lymphocytes and monocytes by activated platelets [55].

Gefitinib Accumulation in Glioblastoma Tissue: Several mechanisms converge to achieve high drug accumulation in glioblastoma tissue [56-57]:

- The small size of Gefitinib facilitates tumor access by diffusion
- High water solubility enables thermodynamic retention inside the malignant cells
- Low CYP3A4 activity in glioblastoma tissue, the main enzyme for Gefitinib catabolism reduces metabolic elimination of Gefitinib.

Binding of Gefitinib (ZD1839) to Human Plasma Proteins: Gefitinib binding in human plasma is extensive (96.6%). In cancer patients, the Pharmacokinetics of total/unbound Gefitinib is highly variable [58].

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer (NSCLC) to Gefitinib: It was observed that somatic mutations were identified in patients with Gefitinib responsive lung cancer in the tyrosine kinase domain of the EGFR gene in eight of nine patients and as compared with none of the seven patients with no response. Mutations were identified as either small in-frame deletions or amino acid substitutions assembled around the ATP-binding pocket of the tyrosine kinase domain. Same mutations were observed in patients suffering from primary non–small-cell lung cancer who had not been given Gefitinib. EGFR mutants manifested augmented tyrosine kinase activity in response to epidermal growth factor and enhanced responsiveness to inhibition by Gefitinib.

Specific mutations in the EGFR gene of patients with non–small-cell lung cancer results in clinical responsiveness to the Gefitinib. These mutations lead to increased growth factor signaling and confer sensitivity to the inhibitor. Screening for such mutations in lung cancers may diagnose

patients who will have a response to Gefitinib [59]. FDA approved Gefitinib for non small cell lung cancer in May 2003. It is marketed in more than 64 countries [61]. Gefitinib is being prescribed in advanced nonsmall cell lung cancer in all lines of treatment for patients entertaining EGFR mutations in Europe since 2009. This description was assumed after Gefitinib proved as a first line treatment to significantly improve survival preventing further amelioration *vs.* a platinum deuce regimen in patients having such mutations [62]. In many countries, Gefitinib has been approved for patients with advanced NSCLC who had received minimum previous chemotherapy once, but its application as a first line treatment in patients with EGFR mutations in progress depends on the latest scientific evidence.

Gefitinib has been approved as first-line treatment for patients with EGFR mutation for ingenuous locally advanced or metastatic and unresectable NSCLC in New Zealand at August 2012 [63]. EGFR mutations are mostly found in the Asian race; women and patients affected with adenocarcinoma. Tests are performed to estimate the level of EGFR. At the time of diagnosis, samples of cancer cells from previous biopsies or surgery may be used to assess the benefit from Gefitinib. The National Institute for Health and Clinical Excellence (NICE) reported the Gefitinib as a first line treatment for patients with metastasized NSCLC that are EGFR positive [64-65].

Directions for Use: Gefitinib is marketed as a lyophilized powder. For a 10 mM stock, 10 mg is reconstituted in 2.24 ml dimethylsulphoxide. The desired therapeutic effect can be produced by using various working concentrations for a desired length of time, but it is typical as a pre-treatment at 0.1-10 μM for 0.5-2 h before treating with a stimulator. It can also be used alone, with varying treatment times lasting up to 24 h [66]. Gefitinib is taken through oral route once daily, with or without food, or as directed by a physician. Absorption of Gefitinib can be decreased by antacids like proton pump inhibitors and H_2 blockers.

This leads to a decrease in the effect of Gefitinib. It is necessary to consult with a physician before consumption of any of these medicines. Intake of Grapefruit or its juice should be avoided in case of patients those are on Gefitinib therapy as it leads to an increase in the side-effects. Gefitinib should be taken at the same time each day [60].

Platelet aggregation in patients was enhanced after Gefitinib administration. So, careful observation is needed for patients with chronic obstructive pulmonary disease, pulmonary fibrosis, and thromboembolic diseases while receiving Gefitinib [36].

Dosage and Administration: The recommended dosage of Gefitinib is 250 mg /day orally with or without food. The dose of 500 mg/day is associated with more side effects, so it is not recommended and although it has the same effect as that of the 250 mg/day. In patient, who experience adverse reactions to the drug as diarrhea or skin rash, the drug should be discontinued for up to two weeks then re-institute therapy should again be re-instituted at the dosage of 250 mg/day.

In hepatic impairment, the drug should be used cautiously, and in case of patients who are receiving potent cytochrome P450 inducers such as rifampicin and phenytoin, the dose must be increased to 500 mg/day. The safety and efficacy of Gefitinib in pediatrics has not documented yet [67]. Higher doses have been reported not to give a better response and to cause an increase in toxicity [68]. For patients who have difficulty in swallowing solids, Gefitinib tablets can be dispersed in non-carbonated drinking water. No other liquids should be used. Tablets are dropped in water and stir until the tablet is dispersed completely without crushing and then drink the liquid immediately. The liquid can also be administered through a nasogastric tube [82].

Dosage Adjustment: Patients with adverse skin drug reactions and those who suffer from untolerated diarrhea which is sometimes associated with dehydration may be auspiciously managed by discontinuing treatment for 14 days followed by rehabilitation of the 250 mg daily dose [69]. Gefitinib therapy should be discontinued if some pulmonary symptoms like dyspnoea, cough, and fever get worsened, and an immediate investigation of these symptoms should be done with appropriate treatment. Gefitinib should be interrupted in patients with diagnosed interstitial lung disease and treated appropriately.

If the symptom of pain in eye develops, then it should be diagnosed and treated appropriately along with the discontinuation of Gefitinib therapy. Abnormal eyelash should be removed if present. The decision of reinstation of 250 mg daily dose should be made after the resolution of eye symptoms and others [68].

If serious adverse effects of the drug are not observed in patients consuming inducers of CYP3A4, *e.g.* rifampicin or phenytoin, then consideration of an increase in a daily dose up to 500 mg as well as monitoring of adverse effects and clinical response should be done. Adjustment of dosage is not required in patients suffering from hepatic impairment because of liver metastases, and not on behalf of patient age, gender, body weight, renal function, and ethnicity [70].

Adverse Effects: The reaction of every person varies accordingly towards cancer treatment. Different peoples experience very few side effects, while others may experience more. The side effects mentioned below are not likely to be affecting everyone getting this treatment. The most common side effects are as follows:

Skin Changes: An acne-like rash on the head, chest, and back is the most common side effect of Gefitinib, which normally commences during the first 2-3 weeks of medication and vanishes once treatment ends. The skin may also become dry and itchy or feel tender and peel. The nails on the hands or feet of some patients become red, sore, and brittle [71]. Some precautions which may help to reduce the severity of skin changes are as follows [72]:

- Use lukewarm water and mild fragrance-free soap for bathing and washing.
- Skincare products containing alcohol should be avoided.
- Anti-acne products impart dryness to the skin, so should not be used.
- Sunlight can make skin symptoms worse. During treatment with Gefitinib, and for several months afterward, the skin gets more sensitive to sun and skin may burn more easily than normal. By applying sun cream with a high sun protection factor (SPF) and cover up with clothing and a hat, the patient can go out in the sun. Sunscreen should not be applied to the skin when radiotherapy is being given to the patient.
- The skin should be moisturized regularly and after bathing.
- The hands and fingernails should be protected from detergents by wearing rubber gloves when washing dishes.

Gefitinib treatment should be discontinued for some days if serious side effects appear to regain the skin [73].

Hair changes: The eyelashes become longer and curly. In men, less growth of beard can be observed. The hair growth of head and body becomes curly, brittle, and fine. Hair loss and thinning of hair develop gradually in some people. These kinds of changes are not permanent as they get improved when treatment is over [72].

Diarrhea: If the patient is suffering from diarrhea, it is necessary to intake plenty of fluids. It can also be controlled with medicine. Counseling with a doctor is important in severe condition [72].

Loss of Appetite: To increase the appetite and to conserve the weight of the patient, guidance from a dietician is important [72].

Nausea and Vomiting: This is not severe, usually. Anti-sickness medicines can be given if it is not controlled [83].

Tiredness: Some people feel weakness and energy reduction in their body while intake of Gefitinib [83]. Bleeding problems: Bleeding from nose, gums or bleeding in urine, vomit, and stool can appear while taking Gefitinib [83].

Eye Problems: On treatment with Gefitinib redness of eyes, dry eyes, itchiness, pain in eyes, infection, and blurred vision can be observed [83].

Sore Mouth: It appears rare approximate 10% [83].

Liver Changes: These kinds of changes are very mild, and as the treatment will end, the liver will become almost normal. Primary clearance of

Gefitinib is done by the liver, so in the case of patients who are suffering from hepatic dysfunction, exposure of Gefitinib is increased. Gefitinib may increase liver enzymes, which could be a sign of liver problems. Patient liver function should be monitored by a doctor using blood tests periodically during treatment. Administration of Gefitinib should be under the supervision of well experienced qualified health professional in the management and treatment of patients with cancer [72, 83].

Severe Lung Problems: Worsening of lung diseases and also death has been reported in some patients receiving Gefitinib treatment. Patients receiving chemotherapy or radiation therapy are more prone to high risk for lung disease. Chances to occur, such problems are only 1%, but if short of breath, high temperature and cough are likely to occur when the patient should contact a physician immediately. Interstitial pneumonia is a very serious side effect of Gefitinib with the frequency of 1-2% [74-75].

Patients consuming either 250 mg or 500 mg as monotherapy for treatment of NSCLC have reported some other side effects at an incidence of <5% are such as amblyopia (2%), vesiculobullous rash (1%), peripheral edema (2%), conjunctivitis (1%), mouth ulceration (1%) and dyspnoea (2%). In patients who are at risk for QT interval prolongation, or with idiopathic pulmonary fibrosis and hepatic impairment, Gefitinib should be used with caution. The use of Gefitinib is contraindicated in cancer patients with negative EGFR mutation [76].

Interactions: Various clinical studies were conducted to determine pharmacokinetic drug interaction with Gefitinib *in-vivo*. Various pharmacokinetic drug interactions with Gefitinib are illustrated in **Table 2**.

- Gefitinib showed no enzyme induction effects in animal studies. Human liver microsome studies demonstrated that in vitro Gefitinib was not a potent inhibitor of any human CYP enzyme activities. At the highest concentration studies, it produced approximately 50% inhibition of CYP2D6 [77]. When Gefitinib was co-administered with metoprolol (a CYP2D6 substrate), a 35% increase in exposure to metoprolol was observed. Caution is advised when co-administered with Gefitinib [70].

- *In-vitro* studies have shown that the Gefitinib is primarily metabolized via CYP3A4. When Gefitinib is co-administered with rifampicin, which is a known potent CYP3A4 inducer, reduction of mean Gefitinib AUC by greater than 80% of that without rifampicin has been noticed in healthy volunteers. Those substances which are inducers of CYP3A4 activity lead to increase metabolism and decrease Gefitinib plasma concentrations. So, co-administration with phenytoin, carbamazepine, rifampicin, barbiturates, hypericum perforatum which are CYP3A4 inducers may reduce efficacy [78].

- Upon administration of Gefitinib with itraconazole (a potent CYP3A4 inhibitor), an 80% rise in the mean AUC of Gefitinib in healthy volunteers was observed. Inhibitors of CYP3A4 Azole antifungals such as ketoconazole and itraconazole, macrolide antibiotics such as erythromycin and clarithromycin, protease inhibitors, grapefruit juice, *etc*. may decrease metabolism and increase Gefitinib plasma concentrations. So, caution should be used when administering CYP3A4 inhibitors with Gefitinib [77, 79].

- When ranitidine is co-administered with Gefitinib at gastric pH above 5, the mean AUC of Gefitinib gets reduced by 47% as found in healthy volunteers [80].

- Plasma concentrations and efficacy of Gefitinib is reduced by drugs, e.g. histamine inducers of CYP3A4 activity lead to increase metabolism and decrease Gefitinib plasma concentrations. So, co-administration with phenytoin, carbamazepine, rifampicin, barbiturates, hypericum perforatum which are CYP3A4 inducers may reduce efficacy [78].

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- When ranitidine is co-administered with Gefitinib at gastric pH above 5, the mean AUC of Gefitinib gets reduced by 47% as found in healthy volunteers [80].
- Plasma concentrations and efficacy of Gefitinib is reduced by drugs, *e.g.* histamine H2-receptor antagonists such as ranitidine or cimetidine; proton-pump inhibitors that cause significant, sustained elevation at gastric pH [51].
- Patients consuming warfarin which are on Gefitinib therapy have reported for bleeding events. So, these patients should be regularly monitored for changes in prothrombin time [51].

TABLE 2: PHARMACOKINETIC DRUG INTERACTIONS WITH GEFITINIB

Agent	Interaction	Management
Histamine H2-receptor antagonists (*e.g.*, ranitidine, famotidine, cimetidine), proton pump inhibitors	Sustained elevation of gastric pH may decrease the plasma level of Gefitinib by 47%	Use with caution [51]
Grapefruit or Grapefruit juice	May inhibit CYP3A4 metabolism of Gefitinib in the intestinal wall and thus increase the plasma level of Gefitinib	Avoid grapefruit and grapefruit juice [70]
Metoprolol	May induce the CYP3A4 metabolism of Gefitinib, declining plasma level of Gefitinib approximately by 83%	None (clinically non-significant) [70]
Rifampicin	May inhibit CYP3A4 metabolism of Gefitinib resulting in a rise in plasma level of Gefitinib by greater than 80%	An increase in Gefitinib dose has been suggested. However, the clinical significance of doing this is unclear [78]
Itraconazole	May decrease the metabolism of Gefitinib and increase Gefitinib plasma concentrations	Use with caution [79]
Warfarin	May increase the anticoagulant effect	Monitor PT or INR closely [51]

CONCLUSION: Gefitinib was the first agent to be tested in clinical trials among tyrosine kinase inhibitors class of anticancer drugs and is a promising antineoplastic agent for the treatment of non-small cell lung cancer. It is more effective, especially in EGFR mutated patients. It inhibits the cellular pathways involved in tumor survival selectively with minimal effect on normal cells. Gefitinib is not recommended for use in pediatric patients, as safety and effectiveness of Gefitinib treatment in pediatric patients has not yet been substantiated. It is necessary to consult with a physician before consumption of other medicines along with Gefitinib. Gefitinib should be taken at the same time each day. Gefitinib is a promising antineoplastic agent for the treatment of non-small cell lung cancer.

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