GEFITINIB

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ABSTRACT

Keywords: gefitinib, EGFR, non-small cell lung cancer.

INTRODUCTION

Gefitinib is a small molecule that specifically inhibits the tyrosine kinase (TK) activity of the epidermal growth factor receptor (EGFR) type 1 by interfering with the adenosine triphosphate (ATP) binding site. About 10% of patient with non-small cell lung cancer (NSCLC) in the US and about 35% in East Asia have EGFR mutations. [1] Hence gefitinib and the other EGFR inhibitor erlotinib are inevitably important in treatment of NSCLC, of the adenocarcinoma variant with the above mutation.

CLINICAL PHARMACOLOGY

DRUG CLASSIFICATION

Antineoplastic, reversible EGFR-TKI. [2] TKI inhibition possibly blocks angiogenesis and cellular proliferation.

MECHANISM OF ACTION

Gefitinib selectively compete for the ATP binding site of the cytoplamic tail of TK domain of the EGFR receptor. [2] This effectively blocks the autophosphorylation of this enzyme domain and subsequently leads to down regulation of downstream pathways which are erstwhile responsible for angiogenesis, metastasis and tumour invasion. It also importantly blocks the anti-apoptotic downstream cascade of the Ras Oncogene.

These numerous cellular biochemical activities are responsible for the very effective ability of Gefitinib to slowdown or inhibit the progression of EGFR positive cancers. On the other hand, after some prolonged exposure to the drug, the cell could potentially circumvent some of these pathways or amplify this receptor to become resistant to the drug. [3]

PHARMACOKINETICS

Absorption	Oral bioavailability, mean: 60% Peak plasma concentration: 3-7 hr Steady-state achieved: 10 days No significant interaction with food intake noted. The use of proton pump inhibitors or H2 receptor antagonists, have been found to slowdown the absorption of Gefitinib.
Distribution	Well distributed in the body with enhanced good tissue absorption and penetration. About 90% bound to protein particularly albumin and alpha 1 acid glycoprotein.

Metabolism	Chiefly metabolised by CYP3A4 (a P450 iso-enyzyme) in the liver to O-desmethyl Gefitinib which is a much less potent derivate of the parent drug.
Excretion	90% faeces Less than 5% urine The remainder in other body fluids or secretions. Half-life is about 28hours. There is incremental accumulation of the drug with continued administration of the drug after 3-4 days.

MECHANISM OF RESISTANCE

Amplification of EGFR gene, gene rearrangements, drug efflux from the cancer cell cytoplasm are all known mechanisms by which the cancer cell evade effects of Gefitinib. [4,5] It has been shown [6] that changes in the phospatidyl inositol-3 kinase –Akt pathway as well as loss of tumour suppressor activity of the PTEN gene both have been identified as clever ways by which the cancer cell develops resistance. Also subtle coexpression of Her2 has been identified as another possible mechanism of resistance.

INDICATIONS

1st line in advanced NSCLC that is EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test**.** [7]

DOSAGES

It is administered as 250mg once day regimen, usually continuous dosing till progression, significant toxicity or side effect develops. [8]

METHODS OF PREPARATION /ADMINISTRATION

Taken orally and comes in once daily regimen. [8]

SPECIAL INFORMATION AND CAUTIONS [9,10]

Contraindications

-Hypersensitivity to the active drug or to its excipients listed below:

<u>Tablet core</u>

Lactose monohydrate

Microcrystalline cellulose (E460)

Croscarmellose sodium

Povidone (K29-32) (E1201)

Sodium lauryl sulfate

Magnesium stearate

<u>Tablet coating</u>

Hypromellose (E464)

Macrogol 300

Titanium dioxide (E171)

Yellow iron oxide (E172)

Red iron oxide (E172)

Elderly

No dose adjustment.

Pediatric

Not established safety or efficacy in this population.

Renal impairment

No dose adjustment if creatinine clearance is > 20 ml/min. Caution should be taken if < 20 ml/min.

Hepatic impairment

Moderate to severe hepatic impairment (Child-Pugh B or C) due to cirrhosis show higher plasmatic concentrations of gefitinib. These patients should be monitored to detect adverse reactions.

Plasmatic concentrations will not increase in patients with AST, alkaline phosphatase or bilirubin due to hepatic metastases.

Immunisations

Live vaccines should not be applied while taking the treatment or for at least 6 months afterwards. Other vaccines can be administered, though may not give as much protection as usual. In any case, it is safe to be in contact with other people who have had live vaccines as injections. There can be problems with oral vaccines. Any contacts with someone who has had oral polio, cholera or typhoid vaccination recently, should be avoided.

Pregnancy

Avoid pregnancy while taking the tablets and at least for two weeks after the last tablet.

Breast-feeding

This should be avoided while taking the medication.

WARNINGS

Ocular disorders

Such as keratitis, aberrant eyelash growth, conjunctivitis, corneal erosion, blepharitis, dry eye. Stop the treatment for severe or worsening ocular disorders.

Skin disorders

Though rare, toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme have been documented. The treatment should be discontinued.

Gastrointestinal perforation

The treatment should be stopped.

Diarrhoea

Severe or persistent diarrhoea has been documented. Drug should be stopped for up to 14 days.

Interstitial lung disease (ILD)

Some few patients may develop ILD, which could be very severe particularly those with background lung diseases such as COPD, pulmonary fibrosis and in smokers. [10]

ILD or ILD-like adverse drug reactions documented are lung infiltration, pneumonitis, acute respiratory distress syndrome or pulmonary fibrosis. If this is confirmed, gefitinib should be permanently stopped.

Hepatotoxicity

Increased ALT, AST, and bilirubin have been reported; These should be monitored and the treatment should be stopped for worsening liver function.

TOXICITIES [11]

Organic system disorders	**Very Common ≥ 1/10**	**Common ≥ 1/1000 to < 1/10**	**Uncommon ≥ 1/1,000 to <1/1000**	**Rare (≥ 1/10.000 a < 1/1.000)**
Renal disorders		Creatinine elevation, proteinuria, cystitis	Haemorrhagic cystitis	
Renal disorders		Haematuria, epistaxis		
Respiratory, thoracic and mediastinal disorders		Pulmonary interstitial disease		
Gastrointestinal disorders	Diarrhoea, vomiting, nausea	Dehydration	Gastrointestinal perforation, pancreatitis	
Hepatobiliary disorders	Elevation ALT	Elevation AST and bilirubin	Hepatitis	
General disorders	Asthenia	Pyrexia		
Nutritional disorders	Anorexia mild to moderate			
Skin and nails disorders		Nail changes, alopecia	Allergic reactions (urticarial, angioedema)	
Eye disorders		Conjunctivitis, blepharitis, dryness	Corneal erosion, aberrant enlargement of eyelashes	Keratitis

DOSE MODIFICATIONS [11,12]

Gefitinib could be stopped for up to 14 days if there are significant toxicities and retried usually at the same dose.

INTERACTIONS

Drugs which induce cytochrome p450 enzymes may reduce the bioavailability or efficacy of the drug. Co-administration of drugs like rifampicin, benzodiazepines and phenytoin could cause reduce bio-availability.

While enzyme inhibitors such as many antibiotics including ciprofloxacin, sulphonamides and antifungal such as Fluconazole could inhibit the metabolism and accentuate the effects of drugs. [5]

CONCLUSION

Gefitinib is an important drug in treatment of EGFR mutated Adenocarcinoma NSCLC. [11] It has significantly improved survival in patients who previously used to have few months to live and often with very poor quality of life. These patients now go on to live longer albeit with a guarded prognosis depending on factors such as disease burden, patient's pre-morbid state and most importantly, the efficacy of the drug in each individual circumstance.

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