

Ceritinib: From Synthesis to Clinical Applications

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Abstract: Lung cancer is the major cause of cancer-related mortality, accounting for over one quarter of cancer deaths. Lung cancers are generally divided into two main categories: SCLC (small cell lung cancer) and NSCLC (non-small cell lung cancer). NSCLC accounts for approximately 85% of all lung cancers. ALK (anaplastic large cell kinase) gene rearrangements are identified and targeted resulting in promising response rates for NSCLC in early studies. Ceritinib is a second-generation ALK inhibitor that has demonstrated activity in crizotinib (the first-generation ALK inhibitor)-resistant patients. In this paper, the synthesis, pharmacodynamics, pharmacokinetics, therapeutic trials, adverse events and drug-drug interactions are briefly overviewed in order to make more scholars, medical workers and patients have a more clear and comprehensive recognition on this drug.

Key words: Ceritinib, non-small cell lung cancer, ALK inhibitor, review.

1. Introduction

Ceritinib is an oral ALK (anaplastic lymphoma kinase) inhibitor synthesized by Michellys' group [1]. The capsule form (Zykadia®) was approved by FDA (Food and Drug Administration) in 2014 [2]. ALK is a receptor tyrosine kinase of the insulin receptor superfamily [3]. The expression of ALK in tissues of health humans is only found in subset of neural cells [4]. The overexpression of ALK acts as a consequence of translocations or point mutations, which have been demonstrated to be an essential oncogenic lesion in a number of cancers especially for Lung cancer [5, 6]. Lung cancer comprises 85% to 90% of cases classified as NSCLC (non-small-cell lung cancer) [7-9]. It has been found that 2~7% of NSCLC tumors express genetic alterations of the ALK genes [10, 11]. ALK-positive tumors are highly sensitive to ALK inhibition, making such aberrations an important target for anticancer drug therapies.

Crizotinib is an anti-cancer drug acting as an ALK inhibitor and approved for treatment of NSCLC in the US and some other countries in 2010s [12, 13]. The undergoing clinical trials verified its safety and efficacy in anaplastic large cell lymphoma,

neuroblastoma, and other advanced solid tumors in both adults and children. However, the resistance to crizotinib has been reported in many patients receiving this agent and typically develops within one to two years of treatment [14]. As a result, the second-generation, oral tyrosine kinase inhibitor was developed to for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. In this paper, the synthesis, pharmacodynamics, pharmacokinetics, therapeutic trials and adverse events are briefly summarized in order to make more scholars, medical workers and patients have a more clear and comprehensive recognition on this drug.

2. Synthesis

The systematic name of Ceritinib is 4-(4-{5-chloro-4-[2-(propane-2-sulfonyl)phenylamino]pyrimidin-2-ylamino}-5-isopropoxy-2-methylphenyl)piperidine-1-carboxylic acid tert-butyl ester [15]. The structure and the synthetic route are shown in Figs. 1 and 2, respectively. The 2-Chloro-4-fluorotoluene is the starting compound for the synthesis of Ceritinib. The 2-Chloro-4-fluorotoluene is treated with H_2SO_4 and KNO_3 under low temperature to give 2-chloro-4-

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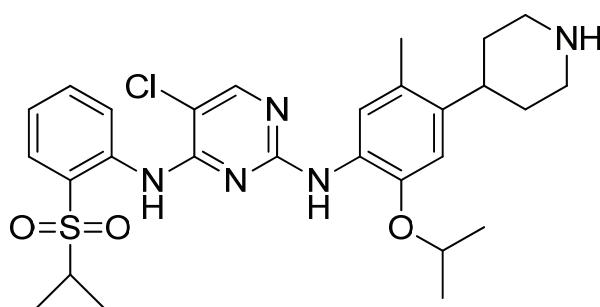


Fig. 1 The chemical structure of Ceritinib.

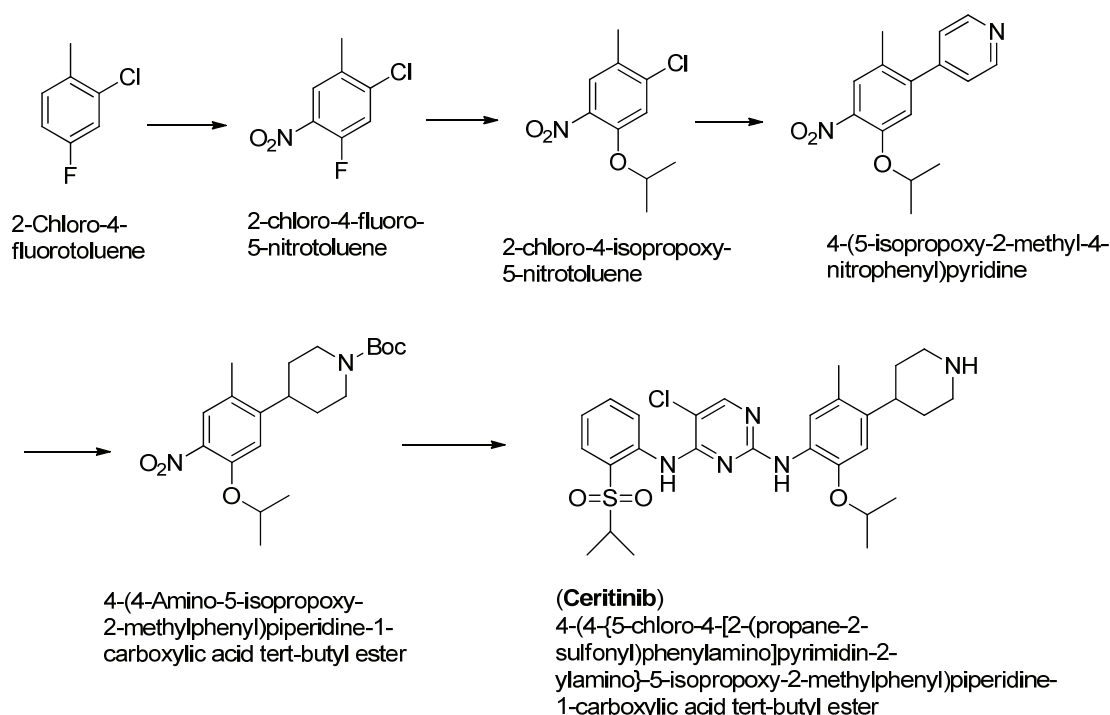


Fig. 2 The synthetic route of Ceritinib.

fluoro-5-nitrotoluene as pale yellow oil and then the oil is reacted with 2-propanol under the catalysis of Cs_2CO_3 to give 2-chloro-4-isopropoxy-5-nitrotoluene. Then the obtained 2-chloro-4-isopropoxy-5-nitrotoluene is mixed with 2-dicyclohexylphosphine-2'-6'-dimethoxybiphenyl with the presence of Pd_2dba_3 and K_3PO_4 under nitrogen atmosphere to achieve 4-(5-isopropoxy-2-methyl-4-nitrophenyl) pyridine as a brown solid. 4-(5-Isopropoxy-2-methyl-4-nitrophenyl) pyridine undergoes a catalytic hydrogenation and then protected by *di*-tert-butyl dicarbonate (Boc_2O) to give 4-(4-Amino-5-isopropoxy-2-methylphenyl)piperidine-1-carboxylic acid tert-butyl ester. The product is mixed with 2,5-dichloro-*N*-(2-(isopropylsulfonyl)-phenyl)

pyrimidin-4-amine and then deprotected to give the final product (ceritinib).

3. Pharmacodynamics

Biochemical and cellular assays showed that ceritinib can inhibit ALK, IGF-1R (insulin-like growth factor I receptor), insulin receptor and ROSI at clinically relevant concentrations [16]. Ceritinib is more active against ALK than other above-mentioned target sites. The *in vitro* and *in vivo* assay results indicated that ceritinib inhibited the autophosphorylation of ALK, ALK-mediated phosphorylation of STAT3 (signal transducer and activator of transcription), as well as the proliferation

of ALK-dependent cancer cells. The anti-tumour activity results showed that the proliferation of cell lines expressing EML4-ALK or nucleophosmin (NPM)-ALK fusion proteins in *vitro* and the growth of EML4-ALK-positive NSCLC xenografts in rodents. In a mouse xenograft tumour model derived from a lung cancer cell line (NCI-H2228) positive for EML4-ALK, complete tumour regression can be tracked after oral administration of ceritinib 25 mg/kg/day. Following treatment with ceritinib 50 mg/kg/day for 14 days, remission was maintained for months in this mouse xenograft tumour model. In addition, the dose of 50 mg/kg/day was effective in several NCI-H2228 tumour models that were resistant to the c-MET/ALK kinase inhibitor crizotinib, suggesting that ceritinib may be active in crizotinib-relapsed patients [17].

4. Pharmacokinetics

Based on recent reports, the maximum serum concentration (C_{\max}) reaches 4–6 h after the oral administration of a single dose [18]. Dose-proportional increases can be tracked in the AUC (area under the curve) and C_{\max} following doses of 50–750 mg/day. The half-life ($t_{1/2}$) of ceritinib is found to be approximately 40 h, and the steady state can be reached in about 15 days. As compared to administration on an empty stomach, the AUC and C_{\max} of ceritinib were 58% and 43% higher following a low-fat meal and 73% and 41% higher following a high-fat meal, respectively. Therefore, when dose is higher than 600 mg taken with food, the ceritinib may have a greater systemic effect than a 750-mg dose taken on an empty stomach, leading to a raised potential for adverse reactions. As 97% of ceritinib is bound to human plasma protein, the volume of distribution following a single oral dose of 750 mg is 4,230 L. Metabolism occurs mostly via

CYP3A (cytochrome P450 3A). Following a 750-mg dose of radiolabeled ceritinib, 92.3% of the dose was recovered in feces and 1.3% was found in the urine. As the drug is primarily eliminated by the liver, moderate to severe hepatic impairment may interfere with clearance. The population pharmacokinetic data collected from 48 patients showed that ceritinib serum concentrations were similar in patients with mild hepatic impairment as compared to those with normal hepatic function. The results also showed that patients with mild to moderate renal impairment have similar exposure to ceritinib as compared to patients with normal renal function.

5. Clinical Trials

An ongoing, single-arm phase I study assessed the safety and efficacy of ceritinib has been reported [18]. 130 patients, 59 in the dose escalation phase and 71 in the expansion phase, were included in this trial. Among them, 94% patients had NSCLC, 3% patients had breast cancer, and 3% patients had other ALK-positive tumors. In all, 68% of the NSCLC participants had received crizotinib prior. Among the NSCLC patients receiving a daily dose of greater than or equal to 400 mg, 1% experienced a CR (complete response), 57% had a PR (partial response), 22% had stable disease, and 11% experienced disease progression.

6. Adverse Events

The most common-adverse events and the relating

Table 1 The most common-adverse events and the relating incidence rates.

Events	Incidence rates (%)
Nausea	82
Diarrhea	75
Vomiting	65
Fatigue	47
Increased ALT level	35

Table 2 The reported drug interactions cases relating to ceritinib.

Drugs	Influence on ceritinib
Rifampin (inducer of CYP3A)	Significant reduction in AUC and C_{\max}
Ketoconazole (inhibitor of CYP3A)	Significant increases in AUC and C_{\max}

incidence rates the in the above-mentioned clinical trial are summarized in Table 1 [18].

7. Drug-Drug Interactions

The coadministration of ceritinib and P-glycoprotein inhibitors or the agents that induce, inhibit, or are substrates of CYP3A or substrates of CYP2C9 often results in drug interactions [19]. Some drug interactions cases are summarized in Table 2 [1].

Therefore, if therapy with a potent inhibitor is medically required, the dose of ceritinib should be reduced. Otherwise, grapefruit and grapefruit juice consumption should also be avoided due to the potential inhibition of CYP3A.

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