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Pharmacokinetics of the Tyrosine Kinase Inhibitor, Alectinib

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Review Article

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Abstract

In 2015, the FDA authorized the use of a new tyrosine kinase inhibitor, Alectinib (ALB), for the intracellular domain of anaplastic lymphoma kinase with exo-cranial pointed mutations. Alectinib became the first drug to be licensed in the first line in August 2017. Its pharmacological properties differ from those of its predecessors, and new research is needed to identify the potential pharmacological and clinical implications. This review presents a critical analysis of the pharmacokinetics of Alectinib and its impact on hepatobiliary metabolism. We present current clinical data and new knowledge that could be developed for further clinical research. With this study, we hope to identify perspectives that can further prolong the efficacy of the anaplastic lymphoma kinase (ALK) tyrosine kinase Alectinib. Tyrosine kinases with receptors for the ligands of platelet growth are a class of enzymes with a key position in the pathogenesis of various molecular alterations that drive idiopathic cancers. The different characteristics of these kinases make them currently a preferential target for the design of new cancer inhibitors. A clear example of their efficiency is the landmark obtained in patients bearing tumors with intronic rearrangements or ALK translocations. These tumors are mostly found in subjects suffering from non-small-cell lung cancer with adenocarcinoma histology and not of the non-smoking type. Moreover, the development of different resistance mechanisms designated allosteric through targeted second-line interventions has culminated in a marked increase in patient survival.

Keywords: Alectinib; Tyrosine Kinase Inhibitors; Pharmacokinetics

Abbreviations

ALB: Alectinib; ALK: Anaplastic Lymphoma Kinase; TKIs: Tyrosine Kinase Inhibitors; NSCLC: Non-Small Cell Lung Cancer; CNS: Central Nervous System; TDM: Therapeutic Drug Monitoring; CPK: Creatine Phosphokinase.

Introduction

Tyrosine kinase inhibitors (TKIs) have markedly improved cancer treatment by specifically addressing molecular abnormalities that promote tumor progression [1]. Rearrangements of the anaplastic lymphoma kinase (ALK) gene are recognized as significant oncogenic drivers in a subset of patients with non-small cell lung cancer (NSCLC), resulting in the development of ALK inhibitors as a targeted therapeutic strategy [2]. Alectinib, a second-generation ALK inhibitor, has been demonstrated to be an effective and selective treatment for ALK-positive non-small cell lung cancer (NSCLC). Initially, it received approval for patients who had either progressed on or were intolerant to crizotinib, the first-generation ALK inhibitor. However, it has subsequently shown superior efficacy as a first-line treatment option [3]. Alectinib's CNS penetration and favorable safety profile reinforce its significance in the management of advanced NSCLC [4]. Comprehending the pharmacokinetics

of Alectinib is essential for enhancing its clinical application. The pharmacokinetic properties of a drug determine its absorption, distribution, metabolism, and excretion, subsequently impacting its efficacy and safety profiles [5]. This review provides an overview of the pharmacokinetic characteristics of Alectinib, discusses factors influencing its pharmacokinetics, and explores the implications of these properties in clinical practice. This analysis aims to inform healthcare professionals regarding optimal dosing strategies and considerations for special populations.

Chemical and Pharmacological Profile of Alectinib

Chemical Structure and Properties

Alectinib is a selective, orally administered inhibitor of anaplastic lymphoma kinase (ALK), characterized by the molecular formula $C_{30}H_{34}N_4O_2$ and a molecular weight of approximately 482.63 g/mol [6,7]. The compound features a complex fused-ring structure that enhances its potency and selectivity for ALK kinase domains [8]. Alectinib is physicochemically defined by its lipophilicity, enabling it to traverse the blood-brain barrier and attain therapeutic concentrations in the central nervous system (CNS) [9]. Its solubility is influenced by pH, demonstrating increased solubility in acidic conditions, which is significant for its absorption in the gastrointestinal tract [6]. Stability studies demonstrate that Alectinib exhibits kinetic stability across various pH levels, thereby improving its appropriateness for oral administration [10].

Mechanism of Action

Alectinib selectively inhibits the ALK tyrosine kinase receptor, which is aberrantly activated in certain non-small cell lung cancers due to genetic rearrangements [11]. By binding to the ATP-binding site of the ALK enzyme, Alectinib inhibits autophosphorylation and downstream signalling pathways that facilitate cell proliferation and survival [3]. This inhibition results in apoptosis and reduced tumor growth in ALK-positive cancer cells. Alectinib has shown effectiveness against multiple ALK resistance mutations that arise during treatment with first-generation ALK inhibitors such as crizotinib. The capacity to surmount these resistance mechanisms is ascribed to its elevated binding affinity and selectivity for mutant ALK proteins [12].

Indications for Therapy

Alectinib has received approval as a first-line therapy for individuals diagnosed with ALK-positive, metastatic non-small cell lung cancer (NSCLC) [13]. Clinical trials, including the ALEX study, demonstrate that Alectinib markedly enhances progression-free survival and overall survival relative to crizotinib. The drug demonstrates efficacy in patients with CNS metastases, a frequent complication in ALK-positive NSCLC, owing to its effective CNS penetration [14]. Although Alectinib is primarily approved for non-small cell lung cancer (NSCLC), current research is investigating its potential off-label uses in other ALK-driven malignancies, such as pediatric cancers and specific lymphomas. Combination therapies involving agents such as bevacizumab are currently being studied to improve therapeutic efficacy [15].

Pharmacokinetic Properties of Alectinib

Absorption

Alectinib is taken orally and demonstrates varied absorption affected by its physicochemical characteristics. Its solubility is contingent upon pH, exhibiting increased solubility under acidic conditions, which is pertinent to its absorption in the gastrointestinal system [6]. The bioavailability of Alectinib is augmented when consumed with food, especially high-fat meals, which can elevate its systemic exposure and promote therapeutic efficacy [16]. Research indicates that the formulation of Alectinib using cyclodextrin inclusion complexes might markedly enhance its solubility and dissolution rate, consequently improving oral bioavailability [10].

Distribution

Following absorption, Alectinib demonstrates significant tissue distribution attributable to its strong lipophilicity. It possesses a substantial volume of distribution and exhibits a strong affinity for plasma proteins, predominantly albumin [17]. Alectinib successfully traverses the blood-brain barrier, attaining therapeutic levels in the central nervous system (CNS), which is essential for addressing CNS metastases in ALK-positive non-small cell lung cancer (NSCLC) patients [18]. The ability to penetrate the central nervous system is a notable advantage compared to certain first-generation ALK inhibitors, which exhibit restricted effectiveness against brain metastases [19].

Metabolism

Alectinib is predominantly metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4. The principal active metabolite, M4, has comparable potency and efficacy against ALK tyrosine kinase as the parent molecule. Alectinib and M4 both enhance the overall treatment efficacy. Genetic differences in CYP3A4 activity may impact the metabolic rate of Alectinib, potentially altering medication concentrations [20,21]. Figure 1 shows the metabolic pathways of Alectinib.

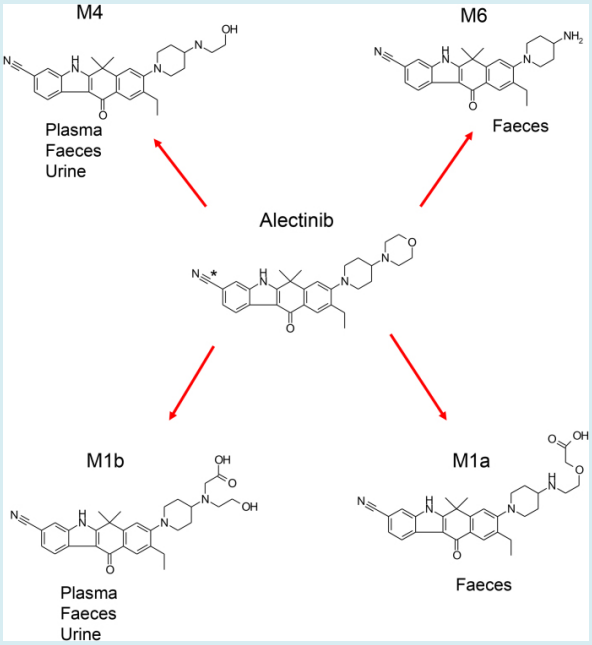

Figure 1: Metabolic pathways of Alectinib [21].

Elimination

Alectinib and its metabolites are primarily excreted through feces, representing around 98% of the given dose, while renal excretion is negligible. The elimination half-life of Alectinib is approximately 32.5 hours, justifying a twice-daily dosage schedule to sustain therapeutic plasma levels. Steady-state plasma concentrations are generally attained within seven days of uninterrupted administration. In individuals with hepatic impairment, reduced metabolic capacity may result in increased systemic exposure, requiring vigilant monitoring and possible dose modifications [22-25].

Factors Influencing Pharmacokinetics

Patient-Specific Factors: Age, Sex, and Genetic Variations

Factors specific to the patient, including age, gender, and genetic polymorphisms, can significantly affect the pharmacokinetics of Alectinib. Alectinib demonstrates efficacy in diverse age groups; however, elderly patients may present altered pharmacokinetic profiles due to age-related physiological changes that influence drug absorption, distribution, metabolism, and excretion [26]. Gender differences in Alectinib pharmacokinetics have not been significantly observed; however, additional studies may be required to definitively assess any potential effects [27]. Genetic polymorphisms, especially in enzymes such as CYP3A4 and CYP3A5 that are critical for drug metabolism, influence the metabolism rates of Alectinib. Genetic variations can result in individual differences in drug exposure and efficacy. Pharmacogenomic testing in personalized medicine may optimize Alectinib therapy for improved outcomes [28].

Hepatic and Renal Function Impairment

Alectinib undergoes primary metabolism in the liver; consequently, hepatic impairment may result in elevated plasma levels of the drug and its active metabolites. Individuals exhibiting moderate to severe hepatic dysfunction may necessitate dosage modifications to avert toxicity. Clinical studies indicate that mild hepatic impairment does not significantly affect Alectinib exposure; however, caution is warranted for individuals with more severe impairment [29]. The renal excretion of Alectinib is minimal, representing less than 1% of the administered dose. Thus, renal impairment is expected to have minimal influence on the pharmacokinetics of Alectinib. Patients with severe renal dysfunction require close monitoring; however, dose adjustments are typically unnecessary [30].

Drug-Drug Interactions

Interaction with CYP Inhibitors and Inducers

Alectinib undergoes metabolism via CYP3A4 enzymes, rendering it vulnerable to interactions with medications that inhibit or induce this metabolic pathway [31]. The concurrent administration of potent CYP3A inhibitors, such as ketoconazole and ritonavir, may elevate Alectinib plasma concentrations, which could improve therapeutic outcomes while also heightening the likelihood of adverse effects. Conversely, CYP3A inducers such as rifampin and carbamazepine may lower Alectinib concentrations, which could diminish its therapeutic efficacy [32].

Clinical management may require dose adjustment of Alectinib when co-administered with CYP3A modulators or the selection of alternative medications with reduced interaction potential. Healthcare providers must evaluate patients' medication regimens to identify and address potential drug-drug interactions [33].

Impact of Concurrent Medications

In addition to CYP3A modulators, other concurrent medications may affect the pharmacokinetics of Alectinib. Drugs that modify gastric pH, like proton pump inhibitors, may potentially influence Alectinib absorption because of its solubility dependence on pH [6]. Current evidence indicates that these interactions lack clinical significance [10]. The combination of Alectinib with other anticancer agents may result in pharmacokinetic and pharmacodynamic interactions. Current investigations are examining the safety

and effectiveness of combination therapies, necessitating meticulous observation for adverse effects and therapeutic outcomes [34].

Disease States: Influence of Disease on Pharmacokinetics

Disease states can modify physiological functions that influence drug pharmacokinetics. In patients with advanced non-small cell lung cancer (NSCLC), malnutrition, organ dysfunction, and concurrent illnesses may affect the absorption and metabolism of Alectinib [35]. Hepatic metastases can compromise liver function, thereby influencing the metabolism and clearance of Alectinib. Inflammation related to cancer may influence the expression of drug-metabolizing enzymes and transporters, potentially affecting the pharmacokinetics of Alectinib [26]. These changes may require modifications in dosing or enhanced monitoring to ensure therapeutic efficacy while reducing toxicity.

Pharmacokinetics in specific populations may demonstrate distinct characteristics. Patients with central nervous system (CNS) metastases benefit from Alectinib's effective penetration of the blood-brain barrier. CNS involvement may influence drug distribution and clearance. Patients exhibiting resistance to previous ALK inhibitors may necessitate increased doses or alternative dosing strategies of Alectinib to attain optimal therapeutic concentrations [36]. Ethnic and racial differences can affect pharmacokinetics as a result of genetic variability in metabolic enzymes and transporters [37].

Clinical Pharmacokinetics and Dosing Strategies

Dose Optimization and Standard Dosing Regimens

Alectinib is indicated for the treatment of patients with ALK-positive advanced non-small cell lung cancer (NSCLC) at a recommended oral dosage of 600 mg administered twice daily with food [38]. The dosing regimen was determined through clinical trials that showed its efficacy and tolerability, resulting in sustained ALK inhibition and enhanced patient outcomes relative to first-generation ALK inhibitors [14].

The dosing schedule of twice daily is consistent with the pharmacokinetic characteristics of Alectinib, which has an elimination half-life of about 32.5 hours and reaches steady-state plasma concentrations within seven days of continuous administration [39].

Adjustments of Dosage in Specific Populations

Modifications to the dosage may be required for patients who encounter adverse reactions or have hepatic impairment. For grade 3 or 4 adverse events, the dosage may be decreased to 450 mg administered twice daily, with a potential further reduction to 300 mg twice daily if required. Individuals with moderate hepatic impairment exhibit heightened exposure to Alectinib, necessitating vigilant monitoring and possible dose modifications to reduce toxicity [40]. Renal impairment minimally affects Alectinib pharmacokinetics because of its low renal excretion, and dose adjustments are typically unnecessary for patients with mild to moderate renal dysfunction. Data regarding patients with severe renal impairment are limited, necessitating caution in their treatment [26].

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) of Alectinib is infrequently utilized in clinical practice, mainly because of its predictable pharmacokinetic characteristics and broad therapeutic index [41]. In specific clinical situations, such as anticipated significant drug-drug interactions or in patients with organ dysfunction, TDM can offer essential insights for optimizing dosage [26]. Plasma concentrations of Alectinib and its active metabolite M4 may correlate with clinical response and adverse effects; however, additional studies are required to confirm their effectiveness as surrogate endpoints [42]. Monitoring ALK mutation status and the emergence of resistance mutations via liquid biopsies can inform treatment decisions and adjustments [14,36].

Safety and Tolerability Profile

Alectinib is generally well-tolerated in patients with ALK-positive non-small cell lung cancer (NSCLC), but like all medications, it is associated with certain adverse effects, some of which are related to its pharmacokinetic properties. Understanding these adverse effects is crucial for optimizing treatment and ensuring patient safety. The most frequently reported side effects of Alectinib include fatigue, constipation, edema, myalgia, and gastrointestinal disturbances such as nausea and diarrhea [2,5].

These adverse events are generally mild to moderate in severity and can often be managed without dose modification [38]. Fatigue is the most common symptom, experienced by a significant proportion of patients, potentially due to Alectinib's central nervous system penetration [26]. Gastrointestinal side effects may be related to the drug's absorption and metabolism in the gastrointestinal tract.

Serious Adverse Events

Serious adverse events associated with Alectinib are less common but require prompt attention. These include

hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, bradycardia, and elevations in creatine phosphokinase (CPK) levels [39].

- **Hepatotoxicity:** Elevated liver enzymes (AST and ALT) have been observed and may necessitate dose adjustments or interruption [43].
- **Interstitial Lung Disease/Pneumonitis:** Although rare, ILD can be severe and potentially fatal. Patients presenting with new or worsening pulmonary symptoms should be evaluated promptly [44].
- **Bradycardia:** Decrease in heart rate has been reported. Monitoring of heart rate and blood pressure is recommended during treatment [37].
- **Elevated CPK Levels:** Increases in CPK may indicate muscle injury; patients may experience myalgia or muscle weakness. Regular monitoring of CPK levels is advised [37].

Pharmacokinetics in Comparison with Other Tyrosine Kinase Inhibitors

Comparison with First-Generation ALK Inhibitors

Crizotinib was the inaugural ALK inhibitor authorized for the management of ALK-positive non-small cell lung cancer (NSCLC). Crizotinib exhibited initial efficacy; however, its limitations, especially concerning central nervous system (CNS) penetration and resistance development, were subsequently identified [45]. Alectinib, a second-generation ALK inhibitor, was designed to address these challenges. Pharmacokinetic studies have shown that Alectinib has a more favorable absorption and distribution profile compared to crizotinib. Alectinib demonstrates enhanced bioavailability and superior CNS penetration attributed to its increased lipophilicity and capacity to circumvent efflux transporters at the blood-brain barrier [46]. This leads to enhanced effectiveness against CNS metastases, frequently observed in ALK-positive NSCLC patients [14]. Alectinib exhibits a longer half-life compared to crizotinib, facilitating sustained ALK inhibition and enabling convenient twice-daily dosing [5]. The shorter half-life of crizotinib requires continuous dosing to sustain therapeutic levels, potentially leading to variability in plasma concentrations and therapeutic outcomes.

Enhanced Central Nervous System Penetration

Alectinib demonstrates superior CNS penetration compared to crizotinib, representing a significant advantage. Research indicates that Alectinib attains elevated levels in CNS tissues, thereby effectively addressing and preventing CNS metastases [14]. The blood-brain barrier frequently restricts the effectiveness of tyrosine kinase inhibitors; however, Alectinib's physicochemical characteristics enable it to surpass this barrier. Clinical trials have demonstrated the central nervous system efficacy of Alectinib. The ALEX study indicated reduced rates of CNS progression in patients administered Alectinib relative to those treated with crizotinib [14]. This underscores the clinical importance of Alectinib's pharmacokinetic benefits in the treatment of CNS disease.

Decreased Toxicity

Alectinib exhibits pharmacokinetic properties that enhance its safety profile relative to crizotinib. Alectinib's selective inhibition of ALK, coupled with its minimal activity against other kinases, results in fewer off-target effects. The metabolism predominantly through CYP3A4 results in predictable pharmacokinetics and a reduced incidence of drug-drug interactions. Patients receiving Alectinib exhibit reduced incidences of gastrointestinal side effects, visual disturbances, and hepatotoxicity in comparison to those treated with crizotinib. The enhanced tolerability contributes to increased patient compliance and improved quality of life.

Efforts to Improve Bioavailability

Enhancing the bioavailability of Alectinib is essential for maximizing its therapeutic efficacy. Majeed BJM, et al. [10] examined the application of β-cyclodextrin and hydroxypropyl β-cyclodextrin inclusion complexes to enhance the solubility and dissolution rate of Alectinib. Their findings demonstrated that these complexes markedly enhanced the oral bioavailability of Alectinib, potentially resulting in more effective dosing strategies and improved patient outcomes. Figure 2 shows the plasma concentration profile of the proposed formula in comparison to free Alectinib in an animal model.

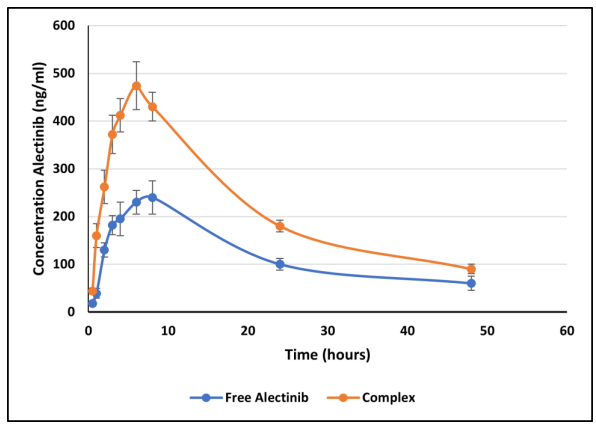

Figure 2: Plasma level-time profile of free Alectinib and cyclodextrine-Alectinib complex in Sprague Dawley rat model showing the difference in Cmax (474 and 240 ng/mL) and Tmax (5.1 and 7.33 h), which are significant for both the 0.05 and 0.1 CI [10].

Madlool DT, et al. [6] investigated the solubility, pH-solubility profile, pH-rate profile, and kinetic stability of Alectinib. Comprehending these physicochemical properties is crucial for the development of new formulations that improve absorption and sustain optimal plasma concentrations [4].

Conclusion

Alectinib is a crucial treatment for ALK-positive NSCLC, primarily due to its superior pharmacokinetic features, including high oral bioavailability, effective central nervous system penetration, and sustained ALK inhibition, outperforming first-generation inhibitors like crizotinib. Clinical trials have demonstrated significant improvements in progression-free and overall survival rates. Understanding Alectinib's pharmacokinetics is key to optimizing its therapeutic use, as factors such as patient characteristics, drug interactions, and disease states influence its absorption, distribution, metabolism, and excretion. Personalized dosing strategies can enhance treatment effectiveness and minimize adverse effects.

While Alectinib generally has a favorable safety profile, monitoring for serious toxicities like hepatotoxicity and interstitial lung disease is vital for timely intervention. Current research is focused on improving its bioavailability, exploring combination therapies to overcome resistance, and using pharmacogenomics for tailored treatments. These advancements promise better patient outcomes and broaden Alectinib's use in oncology. Integrating pharmacokinetic knowledge into practice will be essential for maximizing its efficacy and improving patient quality of life.

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