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Pharmacokinetics of Erlotinib for the Treatment of High-Grade Glioma in a Pediatric Patient with Cystic Fibrosis: Case Report and Literature Review

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Abstract

A 12 year-old female with cystic fibrosis was diagnosed with gliomatosis cerebri after radiographic and biopsy confirmation of the primary intracranial lesion. She was treated with single-agent erlotinib (Terceva®, OSI Pharmaceuticals, Inc., Melville, NY, USA) during and after daily localized radiotherapy. Pharmacokinetic studies were conducted to assess the effect of pancreatic enzyme deficiency and intestinal malabsorption secondary to cystic fibrosis on the bioavailability of orally administered erlotinib, a lipophilic drug. After pharmacokinetic analysis of day 1 and day 8 plasma samples, we concluded that the absorption of orally administered erlotinib was not affected in a cystic fibrosis patient when given concomitantly with pancreatic enzymes replacement therapy.

Keywords

cystic fibrosis; erlotinib; high-grade glioma; pediatric; pharmacokinetic

Introduction

Erlotinib, a highly selective inhibitor of epidermal growth factor receptor (EGFR), has been used in the treatment of several advance malignancies in adults, including non-small cell lung cancer and pancreatic cancer. Several clinical trials are investigating its use in the management of other adult malignancies, including squamous cell carcinomas of the head and neck, ovarian, breast, prostate, colorectal, hepatic and renal cancers.¹ More recently, its use has been investigated in the treatment of malignancies with known over-expression and/or up-regulation of EGFR. EGFR inhibitors are actively being studied in adults with high-grade, refractory gliomas, the most common central nervous system (CNS) malignancy in this age group.² Research into the role of erlotinib, a lipophilic, orally administered EGFR inhibitor in the treatment of CNS malignancies in adults has lead to its investigation in pediatric high-grade glioma.

Patient Case

A 12 year-old female with cystic fibrosis presented to her pulmonologist with a two- to three-week history of altered mental status, confusion, dizziness, distractibility, and change in personality. Her academic performance had notably declined, as well as her ability to process sensory input and verbal communication. After thorough examination and MRI imaging of the head and neck, an extensive intracerebral mass involving the left cerebral hemisphere was discovered. She was referred to the department of neurology/neurosurgery at a regional children's hospital for further work-up. A biopsy performed shortly after referral confirmed the diagnosis of anaplastic astrocytoma.

After diagnosis, the patient was referred to St. Jude Children's Research Hospital for therapeutic management of her malignancy. She was initiated on a non-protocol treatment plan that consisted of single-agent oral erlotinib 150 mg (approximately 120 mg/m²) administered daily along with concomitant daily focal radiation to the site of the tumor. Radiation therapy was discontinued after approximately six weeks, with a total dose of 59.7 Gy administered. The patient continued daily oral erlotinib until the time of disease progression, approximately 4 months after initiating therapy. During the course of her therapy, serial pharmacokinetic studies were performed to identify what effects, if any, her underlying cystic fibrosis and secondary pancreatic enzyme deficiency and intestinal malabsorption would have on the pharmacokinetic profile of erlotinib, a highly lipophilic, orally administered medication. The non-protocol treatment plan, which included the pharmacokinetic studies, was approved by the Institutional Review Board and written informed consent was provided in accordance with institutional and federal guidance.

Pediatric High-Grade Gliomas

Gliomas are the largest group of pediatric neoplasms of the CNS, accounting for approximately 50% of primary CNS malignancies in children. Gliomas that are classified as high-grade comprise 15–20% of all pediatric CNS tumors. They most commonly arise from the brain stem or supratentorial region, however their site of origin is not limited to those particular locations. These high-grade tumors are predominantly astrocytic in origin, and have been known to have poor response to therapy and dismal overall survival outcomes.³ Recent estimates for 5-year survival for pediatric high-grade gliomas range from 10–30%, with survival decreasing dramatically the higher the tumor grade.⁴ The current standard of care for these malignancies includes local control via surgical resection; however tumor location makes tumor removal extremely difficult, if not impossible. The most important independent prognostic indicator for children with gliomas is the degree of tumor resection. Patients who undergo $\geq 90\%$ surgical resection experience improved survival. Therefore, less radical surgical resections translate into poorer overall survival.

After surgical resection, radiotherapy and chemotherapy have also been used in the therapeutic management of high-grade gliomas in children. Radiotherapy is often reserved for children greater than 3 years of age due to the detrimental neuro-cognitive and developmental sequelae associated with its use. In recent years, advanced techniques in the administration of radiotherapy have improved the focal delivery of radiation to the site of the tumor, and its use in children greater than 3 years of age is common practice.^{1,5} While early studies of chemotherapy for children with high-grade glioma appeared promising, overall results with chemotherapeutic regimens have been discouraging. A study published in 1989 by the Children's Cancer Group showed treatment that included chemotherapeutic agents produced some improvement in event-free survival in glioblastoma multiforme. The study compared a 3-drug chemotherapy regimen in combination with radiotherapy versus radiotherapy alone.⁶ Although these findings were encouraging, the results have not been observed in later trials of

both conventional and novel chemotherapy agents. Broniscer et al. conducted two trials of temozolomide, an oral methylating agent, and radiation therapy for brain stem and high-grade gliomas. Although this agent is the standard of care for adult patients with high-grade gliomas, the results of these studies showed no improvement in event-free or overall survival in either type of glioma.^{7,8} Several additional agents and combination chemotherapy regimens have been studied as neo-adjuvant treatment post-resection; however, no gold standard chemotherapy regimen for the treatment of pediatric high-grade gliomas exists.^{9–11} Many treatment modalities for recurrent gliomas have been evaluated, particularly in adult patients, and include agents that target key elements in glial cell proliferation, radio- and chemotherapy resistance, and tumor survival.¹² Unfortunately, these approaches have yet to produce promising results.

Erlotinib for the Treatment of High-Grade Gliomas

Through recent years, a push for research and development of molecular targeted therapies for cancer treatment has spawned the growth of several new anti-tumor classes and agents. Erlotinib is a highly selective, quinazoline-derived, small-molecule EGFR inhibitor. Erlotinib is a member of a larger group of EGFR inhibitors that includes other small-molecule quinazoline derivatives and anti-EGFR monoclonal antibodies. This agent in particular acts as a reversible tyrosine kinase inhibitor that competes with ATP to inhibit EGFR autophosphorylation and the subsequent stimulation of downstream cell processes.¹ It is currently approved for the treatment of advanced, metastatic non-small cell lung cancer and pancreatic cancer in adults. The anti-tumor activity of erlotinib is similar to other anti-EGFR quinazoline-derivatives and monoclonal antibodies, having shown efficacy in the stunting of malignant cell growth, proliferation, invasiveness, and vascularization.

The EGFR pathway has been linked to several processes in the growth and proliferation of numerous types of malignancies. A correlation with EGFR pathway abnormalities, chemoresistance, and poor overall prognosis has also been hypothesized, particularly in studies of non-small cell lung cancer in adults.^{13,14} With regard to gliomas in adults, the EGFR pathway has been linked to tumor cell proliferation, progression, invasiveness and aggressiveness, and survival.^{15,16} The EGFR protein has been found to be over-expressed in up to 85% of pediatric high-grade gliomas, however gene amplification is rare in this population and is more commonly associated with adult high-grade gliomas.³ While no formal correlation has been made between the degree of EGFR expression and prognosis, some studies in adults with glioblastoma multiforme suggest a worse outcome with EGFR overexpression.^{17,18} However, more recent literature suggests that EGFR overexpression alone cannot serve as an independent prognostic factor, noting that adverse outcomes in these patients is most often multi-factorial.^{19,20}

Various abnormalities in the EGFR pathway, including EGFR overexpression, have been associated with pediatric high-grade gliomas. Other pathways with identified genetic abnormalities involved in the manifestation of pediatric gliomas include the p53, phosphatidylinositol 3' kinase (PI3K), retinoblastoma tumor-suppressor gene, and DNA repair pathways. Specifically, the EGFR pathway is linked to several downstream cell processes that facilitate the survival of malignant cells. It is believed that while the EGFR pathway aids in the production and proliferation of normal glial cells, abnormalities in this pathway lead to the malignant transformation of cells, promotion of tumor proliferation, evasion of apoptosis, and tumor survival.^{21,22} Gliomas are extremely vascularized, with abnormalities in the EGFR pathway enhancing malignant angiogenesis via downstream induction of vascular endothelial growth factor (VEGF) production.²³ EGFR over-expression has also been linked to resistance to radiotherapy, a phenomenon researchers were able to induce in murine cell lines that resulted in a marked reduction in cellular radiosensitivity. Investigators also found this could be

reversed by the introduction of an EGFR-inhibiting monoclonal antibody, thus restoring radiosensitivity.²⁴ It has been suggested that some EGFR protein abnormalities may provide insight into the response of some adult gliomas to EGFR inhibitors. In particular, the EGFRvIII variant commonly expressed in glioblastomas in adults has been shown to promote constant signaling of the PI3K pathway, causing uncontrolled proliferation of malignant glial cells. Interruption of this pathway via EGFR inhibition has been shown to induce tumor cell apoptosis. This finding suggests that the presence of EGFRvIII may increase the overall response of malignant glial cells to EGFR inhibitors. A study of 26 adult patients with glioblastoma was done to assess genetic variations in the EGFR protein and their effects on tumor response to either erlotinib or gefitinib, two EGFR kinase inhibitors.²⁵ Of the 26 patients evaluated, 12 were found to have EGFRvIII expression, with 50% of the EGFRvIII positive tumors having response to the EGFR kinase inhibitors. Of the 14 patients who did not express EGFRvIII, only 1 exhibited a response to EGFR kinase inhibition. Based on these findings, the authors concluded that the possession of the EGFRvIII variant provides some degree of sensitization of malignant glial cells to the activity of EGFR inhibitors. However, the response of only 50% of EGFRvIII positive tumors implies that there are several other molecular factors involved in the pathology of gliomas.

Erlotinib Pharmacokinetics

The pharmacokinetic profile of erlotinib, a lipophilic drug with poor solubility in water and methanol, has been extensively studied in adults. After oral administration, erlotinib exhibited approximately 60% bioavailability, with administration with food enhancing bioavailability to upwards of 100%.²⁶ Erlotinib was extensively bound to plasma proteins (95%), and was subject to extensive first-pass hepatic metabolism via the cytochrome P450 3A4 enzyme. Metabolism produced several metabolites, including the active metabolite O-desmethyl erlotinib (OSI-420), and elimination occurs primarily via biliary excretion (63% feces vs. 13% urine). Maximum concentration of the drug (C_{max}) was achieved 2–4 hours after dose administration in adult patients with advanced malignant disease, with a half-life ranging from 10–36 hours.²⁷ The area under the curve (AUC) for erlotinib exhibited inter-patient variability and showed a non-linear dose relationship that has been described in several articles and studies of adult cancer patients.^{28,29}

Very little has been published regarding the pharmacokinetics of erlotinib in children with cancer. Broniscer and colleagues performed pharmacokinetic analysis of both plasma and cerebrospinal fluid (CSF) of an 8-year old child with glioblastoma treated with oral erlotinib. Their results showed modest penetration of erlotinib into the CSF as well as plasma pharmacokinetic data similar to that of published adult studies.³⁰ Pharmacokinetic analysis of 17 pediatric glioma patients enrolled in a Phase I study of erlotinib also revealed steady-state AUC values similar to results produced in adult trials. The authors confirmed no direct correlation between AUC and erlotinib dosage.³¹

The Effects of Cystic Fibrosis on the Pharmacokinetics of Orally Administered Drugs

Cystic fibrosis (CF) is a disease characterized by a dysregulation of electrolytes and fluid secondary to an inability to control ionic chloride and bicarbonate conductance across the cellular membrane. The underlying etiology of this disease is a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome 7. This conductance regulator is an ATP-binding cassette protein located in the sweat glands, lungs, pancreas, intestines, liver, gall bladder, and vas deferens of the male genitourinary system. It is responsible for cyclic-AMP regulated epithelial chloride and bicarbonate trans-membrane conduction. Mutations causing a decrease or lack of activity of CFTR lead to an inability to

excrete intracellular chloride ions and an increase in sodium reabsorption caused by efflux via unregulated epithelial sodium channel activity. This inevitably leads to electrolyte and fluid regulation issues.^{32,33} CF is also associated with the production of thick, viscous secretions caused by excess cellular sodium and chloride. These secretions have the potential to obstruct organs, in particular the lungs, pancreas, liver, intestines, and male genitourinary structures. Obstruction can lead to end-organ damage, including lung tissue scarring, chronic lung inflammation and eventual respiratory failure, decreased pancreatic enzyme secretion secondary to ductal obstruction, intestinal maladies such as intussusception and distal intestinal obstructive syndrome (DIOS), steatosis and cirrhosis of the liver, and infertility in males.^{34, 35}

Absorption of nutrients and orally administered drugs in the gastrointestinal tract is another major concern for patients with cystic fibrosis. This relates to several sequelae of CF including altered gastric pH, gastric motility and transit, potentially modified intestinal permeability and pancreatic enzyme deficiencies.³⁶ Other pharmacokinetic parameters, including drug volume of distribution, plasma protein binding, metabolism, and clearance have also been investigated in patients with CF, particularly with oral antimicrobial agents, anti-inflammatory agents, and immunosuppressants. Beringer and colleagues studied the absolute bioavailability, apparent volume of distribution, and apparent oral clearance of oral azithromycin in 12 CF patients versus healthy volunteers. The results of their study showed that C_{max} , T_{max} , and AUC values were similar between the two study cohorts. They also reported no statistically significant difference in the absorption rate constant (k_a) and absolute bioavailability (F) between the groups. This suggested that absorption of orally administered azithromycin was not impacted by cystic fibrosis. Using a non-compartmental analysis, they concluded that azithromycin pharmacokinetics in CF patients and healthy subjects did not differ.³⁷

The pharmacokinetics of high-dose ibuprofen has been studied in patients with cystic fibrosis, a therapy used to treat the chronic inflammatory process in the lung.^{38–40} Studies have reported lower C_{max} and AUC values as well as greater inter-patient variability in subjects with cystic fibrosis versus healthy subjects. Despite the lower absolute values, both C_{max} and AUC increase in a non-linear fashion in CF patients, as seen with healthy subjects, when increasing doses are administered. Ibuprofen clearance was noted to be significantly more rapid in CF patients compared to healthy subjects when administered identical doses. This may be explained by differences in overall volume of distribution, possible enhanced UDP-glucuronyltransferase activity commonly observed in children with CF, and the potential presence of hyperfiltration resulting from enlargement of the renal glomeruli associated with more severe CF disease.^{41,42}

Scott and colleagues reported the need for increased dosing frequency in order to achieve therapeutic drug levels of cyclosporine, a calcineurin inhibitor used as a post-heart and lung transplant immunosuppressant for patients with CF. They deduced that oral cyclosporine is a highly lipophilic formulation and therefore may be poorly absorbed from the intestines in patients with CF. Increasing dosing frequency led to eventual therapeutic steady state serum concentrations for their post-transplant patients.⁴³ Snell and colleagues assessed the pharmacokinetics of orally administered ganciclovir for cytomegalovirus prophylaxis in post-lung transplant patients with CF. They found the pharmacokinetic parameters investigated were predictable, suggesting that ganciclovir absorption in the gut is independent of factors known to affect drug and nutrient absorption in this patient population.⁴⁴ Touw examined the pharmacokinetic alterations in CF patients treated with various antimicrobial agents. The author found that while protein binding was not altered, clearance for several drugs was increased with a subsequent lowering of serum concentrations and AUCs.³⁶ While these data suggested to investigators variability that exists in the CF population, generalized assumptions

or firm guidelines for predicting the effects of CF on the pharmacokinetics of oral medications have not been made.

Pancreatic enzyme deficiency, specifically lipase and co-lipase, can impact the absorption of lipids, lipid-soluble nutrients, and lipophilic medications. Lipid formulations are often utilized to enhance the bioavailability of oral drug compounds with poor aqueous solubility. In a review of oral lipid-based medication formulations, Hauss examined the nature of lipid formulations and the physiologic factors that must be considered when developing such delivery vehicles, including lipid digestion, drug dispersion, and intestinal permeability.⁴⁵ Zangenberg and colleagues prepared an *in vitro* model of physiologic lipolysis to allow for bioavailability assessment of lipophilic drug formulations. The system mimicked the physiological environment of the gastrointestinal tract by adding porcine-derived pancreatin, a pancreatic lipase, to purified water, a buffer component, bile salts, a calcium-containing solution, and a lipid emulsion.⁴⁶ In a follow-up investigation, the model was shown to adequately simulate physiological conditions when used to assess the aqueous solubility and varying lipophilicity of probucol, an anti-lipid agent, and danazol, a synthetic androgen.⁴⁷ Müller and colleagues examined the oral bioavailability of cyclosporine in a solid lipid nanoparticle formulation. They found that the degradation of the lipid component by intestinal lipase and co-lipase was an integral step in the process of micelle formation and subsequent drug absorption through the cell wall.⁴⁸ Porter and colleagues also attribute the solubility of lipophilic drugs and lipid-based drug formulations to the presence of lipolytic activity at the site of drug absorption.⁴⁹ Both Fatouros and colleagues and Kossena and colleagues directly attribute the process of lipolysis in the intestines to enhanced solubility and absorption of lipid-based drug formulations.^{50,51}

One can reasonably deduce that an alteration in intestinal lipolysis, be it a decrease or complete lack of activity, could negatively affect the solubility and subsequent bioavailability of lipophilic nutrients and oral medications. This was a main concern for the administration of erlotinib, a lipophilic medication, in a patient with an underlying deficiency in pancreatic enzyme activity and intestinal lipolysis. In the setting of cystic fibrosis, gastrointestinal digestion of lipids is altered by the lack of endogenous pancreatic lipase and co-lipase. This obstacle is overcome by exogenous oral supplementation of pancreatic enzymes in the form of pancrelipase or pancreatin. These supplements, available in a number of formulations consisting of varying ratios of lipase, amylase, and protease, are administered with meals to enhance digestion and absorption of fats, carbohydrates and proteins.⁵² Pancreatic enzyme replacement therapy acts to simulate normal gastrointestinal catabolism of these nutrient groups to facilitate physiologic intestinal digestion and absorption of nutrients, lipid-soluble vitamins, and potentially lipophilic drugs.

Methods and Results

Serial blood samples for the measurement of erlotinib and its primary metabolite OSI-420 were obtained post-dose on days 1 and 8 during the first treatment course. Day 1 specimens containing 2 mL per sample were drawn before the dose and at 1, 2, 4, 8, 24, 30, and 48 hours after erlotinib administration. The course 1 day 2 dose of erlotinib was omitted for the purpose of extended pharmacokinetic evaluation. Day 8 blood samples were collected prior to erlotinib administration, then at 1, 2, 4, 8, and 24 hours post-dose. The day 8 samples represented steady-state levels based on population half-life parameters. Samples were collected in heparinized tubes, and the plasma was separated via centrifuge and stored at -80°C while awaiting assay. Erlotinib and OSI-420 concentrations were measured using high-performance liquid chromatography with tandem mass spectrometry.³⁰ A two-compartment model with first-order absorption and elimination was fit to the erlotinib and OSI-420 plasma concentration-time data, and pharmacokinetic parameters were estimated using ADAPTII (version 5).⁵³

The plasma concentration-time profile for erlotinib and OSI-420 was well fit by a two-compartment model (see Figure 1). Erlotinib $C_{\max}$ for day 1 was 1440 ng/mL with an AUC of 18.8 mcg*h/mL. The day 8 erlotinib $C_{\max}$ was 1460 ng/mL with an AUC of 25.7 mcg*h/mL. The rate of erlotinib absorption (k_a) for this patient was 1.51 hr⁻¹. Apparent volume of distribution and clearance of erlotinib was 60.4 L (47.6 L/m²) and 4.9 L/h/m², respectively. These values were similar with those reported in the Broniscer et al. report of plasma and CSF erlotinib pharmacokinetics in a child with glioblastoma.³⁰ The results are also comparable to pharmacokinetic parameters, specifically $C_{\max}$ and AUC data, reported in published erlotinib studies involving adult cancer patients.^{29, 54, 55} A summary of these findings is provided in Table 1.

Discussion

Based on the pharmacokinetic parameters established for this patient, it was determined that the patient's underlying cystic fibrosis did not overtly affect the pharmacokinetic parameters of orally administered erlotinib. Of note, the patient was actively taking the supplement therapy prescribed for her pancreatic enzyme deficiency. It was decided that the pharmacokinetic studies would be performed under everyday conditions, which included the consumption of pancrelipase with meals and snacks. Pancreatic enzyme replacement therapy is an integral part of the therapeutic regimen for CF patients, and therefore pharmacokinetic studies performed without enzyme supplementation would not accurately account for the manner in which this patient or any other patient with cystic fibrosis would take this medication on a daily basis. On both study days she received a 4 tablet dose of pancrelipase with breakfast approximately one hour prior to the administration of erlotinib. It was not possible to determine if the absence of the pancreatic enzyme replacement therapy would have reduced the bioavailability or altered the pharmacokinetics of erlotinib (a lipophilic drug).

The various disease characteristics of cystic fibrosis have been shown to alter the pharmacokinetics of select orally administered drugs. A lack of lipolysis in the gastrointestinal tract may further complicate the solubility and bioavailability of lipophilic drugs or lipid-based oral drug formulations. Altered intestinal bioavailability may warrant the use of higher or more frequent dosing of some medications; however, this phenomenon is not consistent throughout the cystic fibrosis patient population and therefore cannot be made a steadfast recommendation. After a thorough analysis of erlotinib pharmacokinetics in this patient, we found that the absorption of orally administered erlotinib, a highly lipophilic drug, was not affected in this cystic fibrosis patient when given concomitantly with pancreatic enzymes replacement therapy.

Conclusion

The patient case and the accompanying literature review provide evidence for the importance of careful consideration and monitoring of drug therapy for patients with cystic fibrosis. Many factors should be taken into account when prescribing oral drug therapy in this population, including specific pharmacologic properties and gastrointestinal pharmacokinetics of the medication. Our recommendation for the management of oral erlotinib and other lipophilic oral medications in pediatric patients with cystic fibrosis is the continuation of pancreatic enzyme supplementation while the patient is taking the medication, the utilization of therapeutic drug monitoring via plasma concentration levels when feasible, and careful and close observation for therapeutic response, side effects and potential toxicities.

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Figure 1.
Cystic fibrosis patient's erlotinib plasma concentrations on days 1 (A) and 8 (B) and OSI-420 plasma concentrations on days 1 (C) and 8 (D)

Table 1
Comparison of pharmacokinetic parameters of oral erlotinib for children and adults

Pediatric Data	CL _{ERL} (L/h)	Vd _{ERL} (L/m ²)	ka (h ⁻¹)	Day 1 AUC _{ERL} (mcg·h/mL)	Day 8 AUC _{ERL} (mcg·h/mL)	Day 1 C _{max} (ng/mL)	Day 8 C _{max} (ng/mL)
Broniscer A, et al. ⁵⁶ Dose = 120 mg/m ² /day Results for CL _{ERL} , Vd _{ERL} , and ka are an average of Day 1 and Day 8 values. (Range given in parentheses)	4.0 (1.4–7.9)	74.6 (22.8–108.2)	0.59 (0.09–3.5)	22.6 (18.2–27)	29.5 (12–47)	1260 (490–2020)	1827 (943–2970)
Broniscer A, et al. ³⁰ Dose = 70 mg/m ² /day	---	---	0.59	19.4	32.6	---	---
Cystic Fibrosis Patient Case Results Dose = 120 mg/m ² /day	5.7	60.4	1.51	18.8	25.7	1440	1460
Adult Data							
Hidalgo M, et al. ²⁹ Dose = 150 mg/day	---	---	---	16.54 ± 11.02	---	1136 ± 865	---
Prados M, et al. ⁵⁵ Dose = 150 mg/day	---	---	---	19.4 ± 10	---	1340 ± 830	---

CL = clearance; ERL = erlotinib; Vd = volume of distribution; ka = absorption rate constant; AUC = area under curve; C_{max} = maximum plasma concentration