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LETTER TO THE EDITOR

Erlotinib-related rhabdomyolysis: the role of pharmacogenetics and drug–drug interaction

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Introduction

Erlotinib is a small molecule which inhibits the tyrosine kinase activity of the epidermal growth factor receptor (EGFR). Erlotinib, at a standard daily oral dose, is licensed for the treatment for non-small cell lung cancer (NSCLC) patients and is well tolerated. Majority of adverse events are of mild intensity and generally well manageable and reversible. The most common reported adverse effects are skin rash and diarrhea [1–4]. Rhabdomyolysis is a well-known clinical syndrome of muscle injury associated with myoglobinuria, electrolyte abnormalities, and often acute kidney injury. It has been frequently reported in association with the use of lipid-lowering agents, alcohol, and drugs, but is an uncommon complication of antineoplastic treatment [5–8]. However, cases of rhabdomyolysis have been described in patients treated with imatinib and, up to now, only one case in patient treated with erlotinib alone [9, 10].

Erlotinib is mainly metabolized by cytochrome P450 (CYP) 3A4 isoenzyme and is transported across different barriers by P-glycoprotein (*MDR1/ABCB1*) and ABCG2 drug transporters; the potential for CYP- and transporter-mediated drug–drug interactions (DDIs) is high, especially with CYP3A4, P-glycoprotein (P-gp), and ABCG2 inhibitors. According to in vitro and in vivo studies, erlotinib is not only the substrate but also a P-gp/ABCG2 inhibitor [11, 12]. Interindividual pharmacokinetic variability of erlotinib is affected not only by the genetic heterogeneity of drug targets, but also by patient's pharmacogenetic background. Published data show higher erlotinib through concentrations at steady state in patients with the *ABCB1* 1236TT-2677TT-3435TT genotypes compared with other groups. Patients carrying these genotypes had a higher risk of developing high grade 2 toxicity (moderate to severe skin rash and diarrhea) [13].

Case presentation

A 59-year-old female, smoker, with no significant medical history was diagnosed with stage IV NSCLC. Histopathology and cytology revealed an adenocarcinoma. The third-line treatment was oral erlotinib (150 mg per day). At the start of this therapy, the patient was stable, with no comorbidities present, and no concomitant medication except oxycodone was given. Based on laboratory findings, kidney, liver, and bone marrow function was normal.

One month after initiation of the erlotinib, patient suddenly developed fatigue and weakness in lower extremities

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with myalgia. Blood chemistry reported elevated serum creatine kinase (CK) 1215 U/L (normal value <153) with CK isoenzyme MM fraction 100 % and myoglobin 98 µg/L (normal value <51). Other possible causes of elevated creatine kinase level such as myocardial infarction, stroke, and other medications were excluded by diagnostic tests and clinical course of the disease. Based on performed diagnostic tests, diagnosis of drug-induced rhabdomyolysis was made (Table 1). Erlotinib was immediately withdrawn. Patient received a continuous intravenous infusion of isotonic saline and furosemide (up to a maximal cumulative dose of 2.0 mg/kg) for forced diuresis. Additional intravenous fluids were added as needed. After adequate hydration and forced diuresis, serum creatine kinase level started decreasing (Fig. 1). Follow-up laboratory tests showed no pathological findings, indicating secondary hepatic or renal impairment (Table 1). One month later, the patient recovered from rhabdomyolysis with no residual weakness of lower extremities and no myalgia.

Table 1 Patient blood and urine studies

	Baseline	Peak	Follow-up
Sodium (mmol/L)	139	140	139
Potassium (mmol/L)	3.7	3.4	4.1
Chlorine (mmol/L)	99	104	103
AST (U/L)	57	54	22
ALT (U/L)	52	41	13
CK (U/L)	203	1215	92
LDH (U/L)	296	299	218
Creatinine (µmol/L)	95	89	85
Dipstick blood	Some	Some	None
Dipstick protein	+1	+1	+1
RBCs in urine	0–2	3–7	0–2

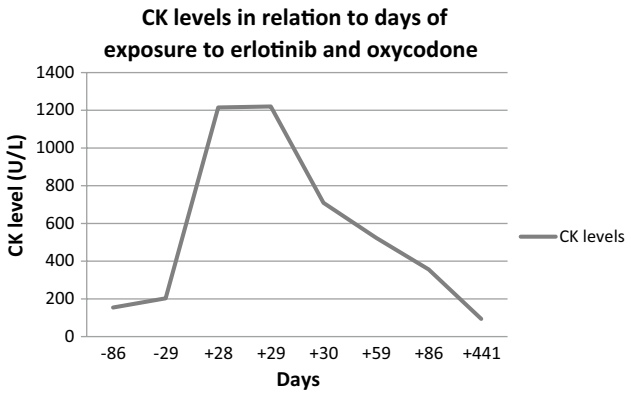

Fig. 1 Creatine kinase levels in relation to days of exposure to erlotinib and oxycodone (day 0 is the day of erlotinib initiation, day +29 is the day when erlotinib was withdrawn; oxycodone was given the whole time)

We suspected rhabdomyolysis was an adverse drug reaction to erlotinib and performed genotyping. Analysis showed that our patient was homozygous for *CYP2C19**2 allele (poor metabolizer) and homozygous for 3435T 2677 T, 1269T alleles in *ABCB1* gene (low transporter activity). The patient was also considered to be extensive CYP2D6, CYP2C9, and CYP3A4 metabolizer (absence of tested variant alleles) and had, according to tested genotype, high ABCG2 transporter activity.

Discussion

Our patient developed rhabdomyolysis 1 month after the initiation of therapy with erlotinib. The temporal relationship between the administration of erlotinib and occurrence of rhabdomyolysis, with regression of signs and symptoms of the disease after the discontinuation, supports the hypothesis that rhabdomyolysis was caused by erlotinib. According to the Karch and Lasagna Adverse Drug Reaction (ADRs) causality assessment, erlotinib-related rhabdomyolysis was rated "probable" [14].

We speculate that two risk factors for erlotinib-induced myopathy were detected in this case.

1. Pharmacogenetic analysis showed that the patient was a carrier of low-activity T alleles within *ABCB1* gene. A previous study has shown that patients homozygous for this allele are at the greatest risk of erlotinib-induced toxicity [13]. Other published data also pointed to the importance of *ABCB1* pharmacogenetics for the kinetics, toxicity, and efficacy of other tyrosine kinase inhibitors [15, 16].
2. Pharmacokinetic DDI could also have contributed to the development of rhabdomyolysis. In our patient, erlotinib was co-administered with oxycodone. Oxycodone is primarily metabolized in the liver by the cytochrome P450 (CYP) enzymes, with CYP3A4 as the major metabolic pathway and CYP2D6 as the minor metabolic pathway, and oxycodone is also a P-glycoprotein substrate [17]. As there is a correlation between P-gp and CYP3A4 substrate specificity, numerous studies have demonstrated clinically relevant drug–drug interactions when a P-gp inhibitor (like erlotinib) is co-administered with a CYP3A4 substrate (like oxycodone) [18]. P-gp participates in the absorption, distribution, and elimination phases and can therefore considerably affect the bioavailability of drugs.

Literature data also suggest that ABCG2 transporter activity could be inhibited by erlotinib [19], therefore increasing the risk of rhabdomyolysis.

The patient also had low capacity for CYP2C19-mediated metabolism. Although we cannot establish direct association with developed side effects since patient did not take any CYP2C19 drug substrate, it could have added to adverse reactions possibly through low capacity for biotransformation of some endogenous substrates.

The presented case suggests that erlotinib may cause rhabdomyolysis in a small proportion of patients who have pharmacogenetic predisposition and take interacting concomitant medication. In our case, interaction occurred on the level of drug metabolism and transport, which considerably prolonged erlotinib biodisposition and resulted in adverse drug reaction.

Up to now, only one case of rhabdomyolysis related to the administration of erlotinib alone has been described in the literature [9].

Conclusion

The described case adds to our knowledge of how a combination of pharmacogenetic and pharmacokinetic factors may lead to the development of erlotinib-induced rhabdomyolysis. Since the risk of developing serious adverse reactions, such as rhabdomyolysis, is low and the cost of genotyping is still high, genotyping all patients before the initiation of erlotinib therapy seems not cost-effective at present. In patients requiring the concurrent use of erlotinib and other drugs, it would be highly advisable—in order to minimize potential DDIs—not to choose drugs which are at the same time CYP3A4 and P-gp substrates. Particularly is important to avoid drugs that act as CYP3A4 and P-gp inhibitors. In the presented case, it is better to choose an analgesic with different metabolic pathways (like morphine) instead of oxycodone which is a CYP3A4 and P-gp substrate.

Important strategy to reduce the incidence of serious erlotinib-induced muscle adverse reaction is patient education to keep adequate hydration status, avoid OTC drugs, and how to identify modifiable risk factors or early signs of rhabdomyolysis.

References

1. Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S (2014) Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 25(Suppl 3):iii27–iii39
2. Steins M, Thomas M, Geißler M (2014) Erlotinib. Recent Results Cancer Res 201:109–123
3. Gridelli C, Maione P, Bareschino MA, Schettino C, Sacco PC, Ambrosio R et al (2010) Erlotinib in the treatment of non-small cell lung cancer: current status and future developments. Anticancer Res 30(4):1301–1310
4. Tiseo M, Andreoli R, Gelsomino F, Mozzoni P, Azzoni C, Bartolotti M et al (2014) Correlation between erlotinib pharmacokinetics, cutaneous toxicity and clinical outcomes in patients with advanced non-small cell lung cancer (NSCLC). Lung Cancer 83(2):265–271
5. SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R (2008) SLCO1B1 variants and statin-induced myopathy-a genomewide study. N Engl J Med 359(8):789–799
6. Zimmerman JL, Shen MC (2013) Rhabdomyolysis. Chest 144(3):1058–1065
7. Mirrakhimov AE, Mirrakhimov EM (2014) Rhabdomyolysis: some extra clues to diagnosis. Chest 145(2):415–416
8. Neyra JA, Rocha NA, Bhargava R, Vaidya OU, Hendricks AR, Rodan AR (2015) Rhabdomyolysis-induced acute kidney injury in a cancer patient exposed to denosumab and abiraterone: a case report. BMC Nephrol 16:118. doi:10.1186/s12882-015-0113-6
9. Moscetti L, Nelli F, Ruggeri EM (2011) Rhabdomyolysis from erlotinib: a case report. Tumori 97(3):415–416
10. Panel N, Blay JY, Adenis A (2008) Imatinib as a possible cause of severe rhabdomyolysis. N Engl J Med 358:2746–2747
11. Marchetti S, de Vries NA, Buckle T, Bolijn MJ, van Eijndhoven MA, Beijnen JH et al (2008) Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCC2 on erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1-/-/Mdr1a/1b-/- (triple-knockout) and wild-type mice. Mol Cancer Ther 7(8):2280–2287
12. Lainey E, Sébert M, Thépot S, Scoazec M, Bouteloup C, Leroy C et al (2012) Erlotinib antagonizes ABC transporters in acute myeloid leukemia. Cell Cycle 11(21):4079–4092
13. Hamada A, Sasaki J, Saeki S, Iwamoto N, Inaba M, Ushijima S et al (2012) Association of ABCB1 polymorphisms with erlotinib pharmacokinetics and toxicity in Japanese patients with non-small-cell lung cancer. Pharmacogenomics 13(5):615–624
14. Karch FE, Lasagna L (1975) Adverse drug reactions—a critical review. JAMA 234(12):1236–1241
15. van Erp NP, Eechoute K, van der Veldt AA, Haanen JB, Reyners AK, Mathijssen RH, Boven E, van der Straaten T, Baak-Pablo RF, Wessels JA, Guchelaar HJ, Gelderblom H (2009) Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J Clin Oncol 27(26):4406–4412
16. Gurney H, Wong M, Balleine RL, Rivory LP, McLachlan AJ, Hoskins JM, Wilcken N, Clarke CL, Mann GJ, Collins M, Delforce SE, Lynch K, Schran H (2007) Imatinib disposition and ABCB1 (MDR1, P-glycoprotein) genotype. Clin Pharmacol Ther 82(1):33–40
17. Zwisler ST, Enggaard TP, Noehr-Jensen L, Mikkelsen S, Verstuyft C, Becquemont L, Sindrup SH, Brosen K (2010) The antinociceptive effect and adverse drug reactions of oxycodone in human experimental pain in relation to genetic variations in the OPRM1 and ABCB1 genes. Fundam Clin Pharmacol 24(4):517–524
18. Bowlin SJ, Xia F, Wang W, Robinson KD, Stanek EJ (2013) Twelve-month frequency of drug-metabolizing enzyme and transporter-based drug–drug interaction potential in patients receiving oral enzyme-targeted kinase inhibitor antineoplastic agents. Mayo Clin Proc 88(2):139–148
19. Shi Z, Peng XX, Kim IW, Shukla S, Si QS, Robey RW, Bates SE, Shen T, Ashby CR Jr, Fu LW, Ambudkar SV, Chen ZS (2007) Erlotinib (Tarceva, OSI-774)antagonizes ATP-binding cassette subfamily B member 1 and ATP-binding cassette subfamily G member 2-mediated drug resistance. Cancer Res 67(22):11012–11020