Pharmacology & Therapeutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors

Tomohiro Terada [a,*], Satoshi Noda [a], Ken-ichi Inui [b]

[a] Department of Pharmacy, Shiga University of Medical Science Hospital, Otsu City, Shiga 520–2192, Japan
[b] Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607–8414, Kyoto, Japan

ARTICLE INFO

Keywords:
Tyrosine kinase inhibitors
Drug transporter
Drug interaction
Therapeutic drug monitoring
Skin disorders

ABSTRACT

Molecular-targeted therapies with tyrosine kinase inhibitors (TKIs) have provided a major breakthrough in cancer treatment. These agents are given orally and demonstrated to be substrates for drug transporters. In clinical settings, TKIs are mainly used at a fixed dose, but wide interpatient variability has been observed in their pharmacokinetics and/or pharmacodynamics. Genetic polymorphisms of ABC transporters, drug-drug interaction and adherence are among the factors causing such variation. To overcome these problems, therapeutic drug monitoring has been applied in clinical practice for patient care. Skin disorders are frequently observed as adverse drug reactions when using TKIs, and are commonly managed by symptomatic therapy based on clinical experience. Recent studies have provided some insights into the molecular mechanisms underlying skin disorders induced by TKIs. This review article summarizes the accumulated clinical and basic pharmacological evidence of TKIs, focusing on erlotinib, sorafenib and sunitinib.

Contents

Abbreviations: ADR, Adverse drug reaction; AUC, Area under the curve; BBB, Blood–brain barrier; BCRP/ABCG2, Breast cancer resistance protein; CNS, Central nervous system; CSF, Cerebrospinal fluid; CGC, Cholangiocarcinoma; CMR, Complete molecular response; EGFR, Epidermal growth factor receptor; GIST, Gastrointestinal stromal tumor; HFSR, Hand-foot skin reaction; HD, Hemodialysis; HCC, Hepatocellular carcinoma; H_2 blocker, Histamine H_2-receptor antagonist; MMR, Major molecular response; MRP2/ABCC2, Multidrug resistance-associated protein 2; NSCLC, Non-small cell lung cancer; OATP, Organic anion transporting polypeptide; OAT3/SLC22A5, Organic anion transporter 3; OCT1/SLC22A1, Organic cation transporter 1; OCT2/SLC22A2, Organic cation transporter 2; P-gp/ABCB1, P-glycoprotein; PDGFR, Platelet-derived growth factor receptor; PFS, Progression-free survival time; PPI, Proton pump inhibitor; QOL, Quality of life; RCC, Renal cell carcinoma; STK10, Serine/threonine kinase 10; STAT3, Signal transducer and activator of transcription; M-2, Sorafenib N-oxide; TDM, Therapeutic drug monitoring; TKI, Tyrosine kinase inhibitor; TTF, Time to treatment failure; UGT, Uridine diphosphate glucuronosyltransferase.

* Corresponding author. Tel.: +81 77 548 2680; fax: +81 77 548 2411.
E-mail address: teradat@belle.shiga-med.ac.jp (T. Terada).

1. Introduction

Recent progress in the development of molecular-targeted agents has expanded the treatment options for patients with various carcinomas, such as lung cancer (Bezjak et al., 2006; Shepherd et al., 2005), renal cell carcinoma (Motzer et al., 2007) and hepatocellular carcinoma (Cheng et al., 2009; Llovet et al., 2008). Molecular-targeted therapies with tyrosine kinase inhibitors (TKIs) are designed to disrupt signaling pathways responsible for the abnormal proliferation of cancer cells, and most TKIs are administered orally. In general, drug efficacy and safety are determined by the interplay of multiple processes that regulate pharmacokinetics (e.g., absorption, distribution, metabolism and excretion) and pharmacodynamics (e.g., drug action). For orally

http://dx.doi.org/10.1016/j.pharmthera.2015.05.009

Please cite this article as: Terada, T., et al., Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors, *Pharmacology & Therapeutics* (2015), http://dx.doi.org/10.1016/j.pharmthera.2015.05.009

administered drugs, pharmacological action is dependent on adequate intestinal absorption and distribution before elimination via metabolic and excretory pathways (Klümpen et al., 2011). Although drug-metabolizing enzymes have been believed to be key determinants of pharmacokinetics, the membrane transport processes mediated by drug transporters are also recognized as important to pharmacokinetic properties.

In clinical practice, oncologists expend substantial effort to treat patients by optimally selecting and dosing TKIs, in order to increase the efficacy and to reduce adverse drug reactions (ADRs). To obtain optimal drug efficacy, pharmacodynamic variations such as gene mutations and the expression levels of certain target molecules [e.g. epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2] have been tested in the practice. To correct for pharmacokinetic variation, traditional cytotoxic chemotherapeutic agents are administered according to the patient's body surface area, even though this approach does not substantially reduce interpatient variability of chemotherapy cytotoxicity (Baker et al., 2002). On the other hand, TKIs are orally given on a daily basis (with or without a drug holiday) at fixed doses, and such fixed dosing may cause much larger variation between individuals in terms of clinical efficacy and toxicity (Gao et al., 2012). It has been widely recognized that renal and/or hepatic functions, genetic background, adherence to treatment and nongenetic factors (drug-drug interactions and drug-food interactions) can cause pharmacokinetic variation of TKIs by changing drug exposure (Klümpen et al., 2011). Among these factors, genetic polymorphism of breast cancer resistance protein (BCRP/ABCG2) has been reported to have a major impact on the drug exposure of many TKIs (Fukudo et al., 2013; Mizuno et al., 2010, 2012, 2014).

Under these circumstances, various efforts to achieve optimal dosing have been attempted, including dose individualization of TKIs, such as phenotype-guided dosing, genotype-guided dosing, toxicity-adjusted dosing and therapeutic drug monitoring (TDM) (Klümpen et al., 2011). Considering applications in clinical practice, TDM is a very promising strategy and recent evidence indicates that certain pharmacokinetic parameters, including trough levels, are correlated with clinical outcomes for many TKIs, such as imatinib, erlotinib, sorafenib and sunitinib (Gao et al., 2012; Yu et al., 2014). Furthermore, the molecular mechanisms of adverse reactions of TKIs have been partly elucidated by basic and *in silico* pharmacology.

It is likely that the pharmacotherapy of TKIs is evolving year by year to resolve the clinical problems in daily practice, by adopting recent basic and clinical pharmacological evidence. This article is focused on reviewing such evidence, concentrating on three kinds of TKI: erlotinib, sorafenib and sunitinib. These drugs have been used as the first-line therapy to treat patients with non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), differentiated thyroid cancer ,and renal cell carcinoma (RCC), and extensive information including on drug transporters affecting their pharmacokinetic variation and the molecular mechanisms of their skin disorders has recently been accumulated.

2. Effect of drug-metabolizing enzymes and transporters

Most TKIs are oral drugs given daily as a single agent at a fixed dose. Oral administration should be processed by intestinal absorption, namely, intestinal influx and efflux steps, which could be mediated by drug transporters. Although it is not necessary to take this process into consideration for classical injectable anticancer agents, the intestinal absorption process should cause large pharmacokinetic variability, probably due to fat content within food, coadministration with gastric acid-reducing drugs and the functional ability of intestinal drug transporters that have recently been identified. In this section, first, we summarize the pharmacokinetic factors that regulate the drug disposition of erlotinib, sorafenib and sunitinib, with an intensive focus on intestinal efflux drug transporters (Table 1).

2.1. Erlotinib

Erlotinib is metabolized in the liver, mainly by cytochrome P450 (CYP) 3A4/3A5 and, to a lesser extent, by CYP1A1/1A2, to produce the active metabolite OSI-420 (desmethyl erlotinib, M14), followed by the formation of many other metabolites, including oxidative metabolites (Li et al., 2007a; Ling et al., 2006). Erlotinib and OSI-420 are considered to be equipotent in inhibiting EGFR tyrosine kinase activity.

In vitro transport studies have demonstrated that erlotinib is a substrate for P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (BCRP/ABCG2), but not for multidrug resistance-associated protein 2 (MRP2/ABCC2) (Elmeliegy et al., 2011; Marchetti et al., 2008). ATP binding cassette membrane transporters, including ABCB1 and ABCG2, are expressed in normal tissues including the small intestine, liver, kidney and blood–brain barrier (BBB) (Glavinas et al., 2004), and are responsible for regulating the oral absorption, biliary and urinary secretion, and penetration of BBB for several anticancer drugs including TKIs (Agarwal et al., 2010; Kodaira et al., 2010; Kunimatsu et al., 2013; Lagas et al., 2010; Mizuno et al., 2012; Oostendorp et al., 2009; Polli et al., 2009). Furthermore, the pharmacokinetic roles of ABCB1 and ABCG2 were also assessed using gene-disrupted mice, namely, *Abcg2*$^{-/-}$, *Abcb1a/1b*$^{-/-}$ and *Abcg2*$^{-/-}$/*Abcb1a/1b*$^{-/-}$ (triple-knockout) mice. When erlotinib was given orally to *Abcg2*$^{-/-}$/*Abcb1a/1b*$^{-/-}$ mice, it was found that its area under the curve (AUC) was about 50% higher in the triple-knockout mice than in wild-type ones (Marchetti et al., 2008). These findings suggest that ABCB1 and ABCG2 play pivotal roles in restricting the intestinal absorption of erlotinib. Further evidence of these transporters' contribution was obtained by pharmacogenomic analyses, which are introduced in Sections 3.1 and 3.2. A recent study has also indicated that erlotinib and OSI-420 are substrates for the uptake transporters organic anion transporter 3 (OAT3/SLC22A5) and organic cation transporter 2 (OCT2/SLC22A2), but their pharmacokinetics and clinical implications have not been fully elucidated (Elmeliegy et al., 2011).

2.2. Sorafenib

Sorafenib is primarily metabolized in the liver, by CYP3A4-mediated oxidation and uridine diphosphate glucuronosyltransferase (UGT) 1A9-mediated glucuronidation. Sorafenib N-oxide (M-2), the major active CYP3A4 metabolite, has been reported to represent approximately 10% of the circulating sorafenib concentration in plasma (Clark et al., 2005).

In vitro transport studies have demonstrated that sorafenib was moderately transported by ABCB1 and more efficiently by ABCG2 (Gnoth et al., 2010; Hu et al., 2009; Lagas et al., 2010; Tang et al., 2013). When sorafenib was orally administered to *Abcg2*$^{-/-}$, *Abcb1a/1b*$^{-/-}$ and *Abcg2*$^{-/-}$/*Abcb1a/1b*$^{-/-}$ mice, the systemic exposure upon oral administration did not differ among all strains. However, brain accumulation was 4.3-fold increased in *Abcg2*$^{-/-}$ mice and 9.3-fold increased in *Abcg2*$^{-/-}$/*Abcb1a/1b*$^{-/-}$ mice (Lagas et al., 2010). This suggests that intestinal ABCB1 and ABCG2 do not play a major role in the oral bioavailability of sorafenib, but are responsible for its brain accumulation.

To understand the hepatic disposition of sorafenib, because this drug is used for HCC, *in vitro* and *in vivo* transport studies were carried out. As a result, organic cation transporter 1 (OCT1, SLC22A1) and organic anion transporting polypeptides OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) were shown to be responsible for the sinusoidal membrane transport of sorafenib (Herraez et al., 2013; Swift et al., 2013; Zimmerman et al., 2013). Clinical pharmacogenomic studies have also demonstrated that hepatic OCT1 may be responsible for the efficacy of sorafenib for HCC (see Section 3.2).

Please cite this article as: Terada, T., et al., Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors, *Pharmacology & Therapeutics* (2015), http://dx.doi.org/10.1016/j.pharmthera.2015.05.009