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Laboratory-Clinic Interface

Variability in bioavailability of small molecular tyrosine kinase inhibitors

Maikel Herbrink [a,*], Bastiaan Nuijen [a], Jan H.M. Schellens [a,b], Jos H. Beijnen [a,b]

[a] Department of Pharmacy and Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Louwesweg 6, 1006 BK Amsterdam, The Netherlands
[b] Department of Pharmaceutical Sciences, Science Faculty, Utrecht University, Utrecht, The Netherlands

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ABSTRACT

Small molecular tyrosine kinase inhibitors (smTKIs) are in the centre of the very quickly expanding area of personalized chemotherapy and oral applicability thereof. The number of drugs in this class is rapidly growing, with twenty current approvals by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). The drugs are, however, generally characterized by a poor oral, and thus variable, bioavailability. This results in significant variation in plasma levels and exposure. The cause is a complex interplay of factors, including poor aqueous solubility, issued permeability, membrane transport and enzymatic metabolism. Additionally, food and drug–drug interactions can play a significant role. The issues related with an impaired bioavailability generally receive little attention. To the best of our knowledge, this article is the first to provide an overview of the factors that determine the bioavailability of the smTKIs.

Introduction

The development of anticancer drugs is a very quickly expanding area in which two trends are clearly present. In the first place new agents are designed fulfilling the requirements for personalized medicine. The advancement of techniques such as (cell-based) high throughput screening and the diverse possibilities in molecular modeling have lead to a therapeutic target-based drug discovery regime [1,2]. Along with the evolution of synthetical methods, compounds are found that are highly specific and demonstrate great affinity for molecular targets [3–6]. Individual tumors, and their specific targets, can be genetically characterized and a suitable 'personalized' chemotherapy can be appointed depending on the neoplasm's genotype [7]. The second movement is also referred to as 'the intravenous to oral switch'. The last decade has shown an increasing number of anticancer drugs that are administered orally [8,9]. Currently, most of the anticancer drugs that are in development or recently approved are destined for oral ingestion. Unlike previous conventions, oral therapy in cancer has proven efficient and less costly [10]. On top of that comes the preference of the patient, especially since oral ingestion can take place in the home setting and is highly convenient compared to intravenous administration [8].

In the middle of these trends stands a promising and growing group of drugs; the tyrosine kinase inhibitors (TKIs). In the past ten years, the size of this group has doubled [11–13]. The TKIs target specific parts of tyrosine kinase receptor proteins that play an important role in the intracellular signaling pathways in tumor cells. Their interference leads to a deregulation of essential cell functions such as proliferation and differentiation [14]. One of the two types of TKIs, the small molecular TKIs (smTKIs) with an intracellular activity, are without exception administered orally. Currently, twenty of these small molecular compounds are approved by both the EMA and the FDA. General information on the drugs is found in Table 1 [11,12]. This review will focus on these particular compounds. The other type of TKI is a group of monoclonal antibodies, which possess a larger molecular structure and interfere with signal transduction by binding extracellularly and are administrated intravenously. The small molecular inhibitors have proven useful in the therapy of certain types and lines of cancer [6,11,12,15]. Additionally, smTKIs may be prescribed as alternatives when other therapeutic options have failed or are not appropriate. Although the development of personalized oral chemotherapy is very promising, the nature of the selection process leads to drugs, however, that are hindered by a low and variable bioavailability (*F*). This aspect and its causes are underexposed subjects in literature. Indeed, smTKIs may be very potent and suitable for certain tumor types. When they are unable to reach their target in sufficient quantities, the therapy will be suboptimal or

* Corresponding author. Tel.: +31 20 512 5008.
E-mail address: Maikel.Herbrink@slz.nl (M. Herbrink).

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Table 1
Overview of the general information on tyrosine kinase inhibitors approved for use by the EMA and the FDA by 1 November 2014.

Drug	Trade name	Primary indication(s)	Oral bioavailability (%)
Afatinib	Giotrif	NSCLC	–[4]
Axitinib	Inlyta	RCC after failure with sunitinib/ cytokines	47–58
Bosutinib	Bosulif	CML when imatinib, nilotinib and dasatinib are not appropriate	–
Cabozantinib	Cometriq	MTC	–
Crizotinib	Xalkori	NSCLC	43
Dabrafenib	Tafinlar	Melanoma	95
Dasatinib	Sprycel	CML	–
Erlotinib	Tarveca	NSCLC, pancreatic cancer	60–76
Gefitinib	Iressa	NSCLC[1]	57–59
Imatinib	Gleevec/ glivec	CML, ALL, CEL, HES, MDS/MPD, GIST, DFSP	98
Lapatinib	Tyverb	HER-2+ breast cancer	–
Nilotinib	Tasigna	CML	30
Pazopanib	Votrient	RCC, STS	14–39 [163]
Ponatinib	Iclusig	CML when imatinib, nilotinib and dasatinib are not appropriate, ALL[2]	–
Regorafenib	Stivarga	CRC, GIST	69–83
Ruxolitinib	Jakavi	CIM, PPVM, PETM	95[5]
Sorafenib	Nexavar	HC, RCC, DTC	–
Sunitinib	Sutent	GIST, MRCC, pNET	–
Vandetanib	Caprelsa	MTC[3]	–
Vemurafenib	Zelboraf	Melanoma	–

ALL, acute lymphatic leukemia; CEL, chronic eosinophilic leukemia; CIM, chronic idiopathic myelofibrosis; CML, chronic myeloid leukemia; CRC, colorectal cancer; DFSP, dermatofibrosarcoma protuberans; DTC, differentiated thyroid carcinoma; GIST, gastrointestinal stromal tumours; HC, hepatocellular carcinoma; HES, hypereosinophilic syndrome; MDS, myelodysplastic disease; MPD, myeloproliferative disease; MRCC, metastatic renal cell carcinoma; MTC, medullary thyroid carcinoma; NSCLC, non-small cell lung cancer; PETM, post essential thrombocythaemia myelofibrosis; PPVM, post polycythaemia vera myelofibrosis; pNET, pancreatic neuroendocrine tumours; RCC, Renal cell carcinoma; STS, soft tissue sarcoma.

[1] Withdrawn in 2005 due to lack of evidence in prolongation of life. Source: European Public Assessment Reports (EPARs), Website FDA and Summaries of product characteristics (SmPCs) of the above mentioned smTKIs, accessed at 20th November 2014.

[2] Changes in usage are suggested by EMA due to life-threatening vascular events.

[3] Approval by EMA was conditional.

[4] Data were not available.

[5] Based on a mass balance study.

even failing. This review will address the bioavailability-determining factors for the smTKIs and presents prerequisites in both the marketed formulations and chemotherapeutical practice to minimize the reduction and variation in oral *F*. It is important to be aware of and understand the various factors that determine *F* and its variability of the smTKIs. This will allow for the betterment of their use in chemotherapy.

Oral bioavailability

The fraction of the total ingested drug that reaches the systemic circulation unchanged, and is transported to its therapeutic target, is defined and termed (absolutely) bioavailable (*F*) [16]. Fig. 1 schematically presents the different processes that govern the extent of *F*. *F* is the product of the drug fraction that is absorbed (F_F), the dose that reaches the hepatic portal vein unchanged (F_G) and the fraction of the dose that is not metabolized by enzymes in the liver (F_H), as presented in Eq. (1) [16,17],

$$F = F_F * F_G * F_H \quad (1)$$

In each of the before mentioned steps, an amount of drug might be lost. Whatever the cause, a low *F* is associated with an increased intra- and interpatient variability in drug plasma concentration [18]. Registration texts and other studies, as far as could be accessed, show significant inter-individual variation in important pharmacokinetic parameters of all smTKIs [19–37]. This may result in possibly dangerous situations for patients that experience extensively low, or high, exposure to the substances. Many anticancer drugs are known to exhibit a small therapeutic window, where the minimum therapeutic dose and the maximum tolerated dose (MTD) are close to each other [38]. The same is true for the smTKIs, with a possible exception of Dabrafenib, Imatinib, Gefitinib and Pazopanib [13,19,39–52]. As a consequence of pharmacokinetic variation, inter-individual differences in therapeutic dose and MTD should be taken into account. Under- and overdosing are thus potential hazards of oral chemotherapy. Thus, careful dose titration and adjustments are required to assure an adequate therapy, in both effect and tolerance. Hence, therapeutic drug monitoring (TDM) is upcoming for smTKIs [38].

The human oral *F* of the smTKIs is largely unknown or inaccessible in the public domain and published values are generally low and the exposure is variable [39,53,54]. The determination of oral *F*-values requires a comparison between oral and IV-administration. IV-solutions with smTKIs are often difficult to prepare due to the poor water solubility of the drugs (see Section 'Dissolution'). Table 1 presents the currently known values. Low values for oral *F* may be due to one or more of several factors. It is often the consequence of a complex interplay of both physicochemical and physiological processes. Furthermore, it may also be influenced by concomitant administration of other drugs. Additionally, the intake of food or certain habits of life-style may exert an impact on *F*.

B(DD)CS-classification

The Biopharmaceutics Classification System (BCS) can aid to clarify possible absorption-related causes of an impaired *F*. Solubility and permeability of a drug are recognized as fundamental parameters in the absorption process [55]. The BCS combines data on the *in vitro* solubility in the intestinal tract of the drug substance and data on the extent of total permeation through the gut wall and appoints a class to it [55–57]. Fig. 2 summarizes the assignment of the classes and presents the classes of the smTKIs [58,59,37]. Classifications may be interpreted as signals for formulation design (class II and IV) or physicochemical modifications (class III and IV) [58].

The newer Biopharmaceutics Drug Disposition Classification system (BDDCS) correlates the passive permeability rate of drug with their metabolic elimination [60–62]. Here, passive permeability is considered 'good' when elimination is largely governed by metabolism (>70%) [63]. Fig. 2 presents the BDDCS classification between braces where it differs from the BCS classification. The discrepancies between the BCS and BDDCS classes may be due to the fact that BCS is based on total permeation and BDDCS on the passive permeability rate [64]. The latter does not account for interaction with membrane transporters.

Pharmaceutical factors (F_F)

Dissolution

The first step in becoming bioavailable is the dissolution of the drug substance into the gastrointestinal fluids. Since only the solute form of the drug can be absorbed, the release from the oral formulation is an important parameter. In fact, the major cause for the different absorption profiles of drugs from various products is