

Editorial

ADME/DMPK in the development and use of tyrosine and serine-threonine kinase inhibitors

Godefridus J. Peters^{*}, Kin Tam⁺

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^{*} Department of Medical Oncology, VU University Medical Center, Amsterdam, the Netherlands. Gj.peters@vumc.nl.⁺ Faculty of Health Sciences, University of Macau, Taipa, Macau. kin_tam@umac.mo.

Since the introduction of the tyrosine kinase inhibitor (TKI) imatinib, for treatment of chronic myeloid leukemia (CML) about 30 new related compounds have been registered by the US FDA, the EMEA and other registration authorities for various types of cancers, both solid tumors and hematological malignancies. Some drugs have also been registered for other diseases, such as inflammation. These compounds do not only target tyrosine kinases, but also serine-threonine kinases [1, 2]. In a recent review we showed that these compounds show a large variation in their physico-chemical properties [3], which affect their ADME properties. In general these small compounds (mostly < 500 kD) are poorly soluble, which may lead to a solubility limited absorption, while uptake through the gut is dependent on protein binding [4]. This leads to a large variability in pharmacokinetics (PK) [5]. It appeared that all these inhibitors obey all common parameters that dictate the variability of PK (Figure 1). Therefore for several of these drugs, it would be better to give them with food; despite this experience pharmaceutical companies often advise to give the drugs without food, leading to an even worse bioavailability [6].

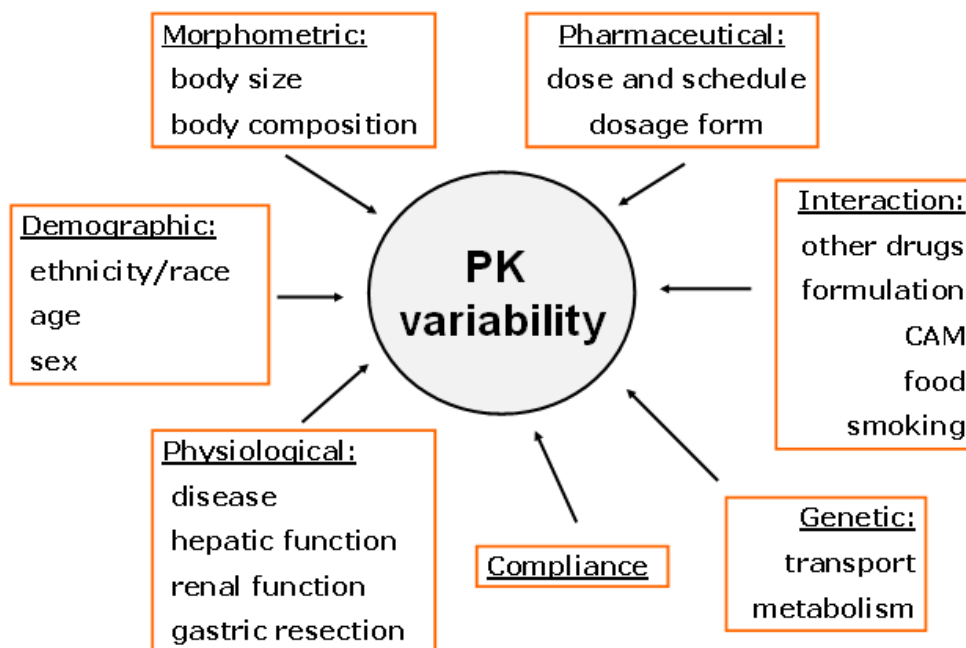


Figure 1. Sources of variability in pharmacokinetics (PK). CAM, complementary and alternative medicine.

Protein kinases play important roles in signal transductions cascades that govern many cellular events (Fig. 2), including cellular stability, selective growth disadvantage or apoptotic cell death [1]. These compounds are often referred to as targeted therapy, since the drugs are designed to inhibit a specific pathway in the cancer cell, usually a pathway which is essential for the cancer cell to survive. This property is often referred to as oncogene addiction. Examples are the above-mentioned imatinib, which is targeted against the Bcr-Abl kinase, which only occurs in CML. Imatinib is also targeted against c-kit, which is specifically expressed in gastrointestinal stromal tumors (GIST). Another early example includes the epidermal growth factor receptor (EGFR) which is increased in adenocarcinoma, a subtype of non-small lung cancer (NSCLC). Adenocarcinomas with an activating mutation in EGFR are sensitive to erlotinib and gefitinib [7]. Another example is the ALK-EML translocation in adenocarcinoma [8], against which crizotinib is targeted. To develop selective TKIs for a particular tumor a thorough understanding of cellular signaling cascades is of utmost importance, not only in the tumor but also in its neighboring stroma, endothelial cells and immune cells such as various macrophage populations. Also, communication between these cells needs to be elucidated. Clearly the research and development along this direction will continue in the coming decades.

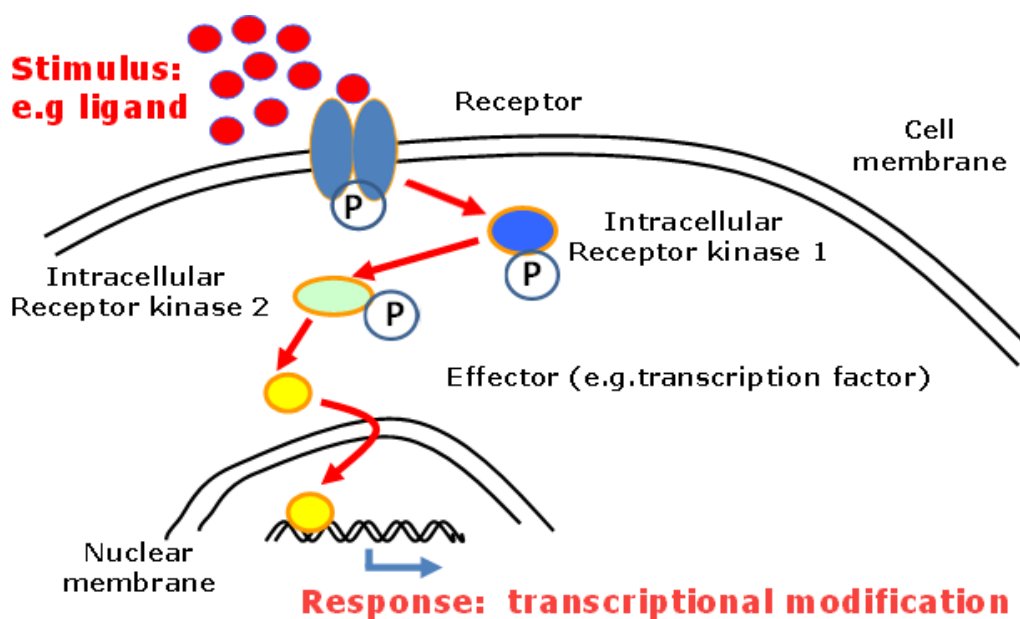


Figure 2. Simplified scheme of the action of a receptor tyrosine kinase. The receptor is stimulated by a ligand, often leading to a dimerization, such as with EGFR. The intracellular tyrosine site is phosphorylated with ATP as the phosphate donor, leading a cascade of signals due to the transfer of a signal to one or more kinases.

Finally the last effector (usually a transcription factor) is activated and passes the nuclear membrane, resulting in a transcriptional modification. A tyrosine kinase inhibitor binds to the ATP binding site resulting in inhibition of this pathway.

In the early discovery / development phases of these compounds, the ADME and DMPK aspects were sometimes neglected, since the focus was often on potency and selectivity against a particular kinase target of interest. For the first TKI to be registered, imatinib, it is now clear that its efficacy is dependent on its pharmacokinetics, a certain trough level (about 1000 ng/ml, about 2 μ M) is associated with a better response, although elevated trough levels (>1500 ng/ml) are associated with toxicity [9, 10]. Also for sorafenib, a multikinase inhibitor of the vascular endothelial growth factor receptor (VEGFR) and the wild-type RAS-Raf pathway, it was shown that the efficacy was related to its pharmacokinetics. Moreover, some of its metabolites are substrates for several influx and efflux pumps [10, 11]. These properties lead to suboptimal efficacy and unexpected toxicity. For some drugs this resulted in development failures in the

late phases. A recent example is the discontinuation of rociletinib [7], an inhibitor of the T790M mutation of EGFR. This T790M mutation commonly develops after treatment with erlotinib or gefitinib. Rociletinib was granted Breakthrough therapy status from the FDA for accelerated development, but in the Phase III trial severe grade 3 toxicity (hyperglycemia) was observed in 22 % of the patients due to inhibition of the insulin-like growth factor receptor (IGFR). Thirty-five percent of the patients had to take a glucose lowering drug (usually metformin). Furthermore some responders could not be verified at an independent evaluation, with a drop in response rate from 59 to 32 %. This compound would have benefited from a more extensive evaluation. Another specific inhibitor of the T790M mutation of EGFR, osimertinib, did not suffer from this problem, and was recently registered by the FDA after a similar Breakthrough therapy status and an accelerated development program.

In this special issue of ADMET and DMPK we intended to illustrate a number of issues important in the development of various protein kinase inhibitors, with a special focus on the ADMET and DMPK aspects of these compounds, and how to properly incorporate the basic ADMET and DMPK information to optimize the design of clinical trials. The papers will be divided between the September and December issues. Thompson *et al* [12] give an overview on the mechanism of action of currently used EGFR and ALK directed compounds, describing the issues mentioned above. Shah [13] describes a less common side-effect of these compounds, cardiovascular toxicity. This type of toxicity is also quite common for several of the chemotherapeutic agents and oncologists usually know how to deal with these patients. According to Shah the hallmark of cardiovascular function, QT aberrations, are often overemphasized. This toxicity was also observed for Rociletinib, but not a reason for its withdrawal. Pott *et al* [14] describe a cross-talk between two signaling pathways. In the forthcoming issue interaction between the cytotoxic drug gemcitabine and the c-Met inhibitor crizotinib will be described, as well as the development of a new formulation for a novel polo-like inhibitor, which had to take into account all above-described problems, such as poor solubility, low permeability and the crystalline nature. Next another paper will focus on an alternate target for ROCK inhibitors, ocular disease. Earlier the anti-angiogenic antibody bevacizumab was already indicated for ocular diseases as well. Other aspects which will receive attention are the role of various efflux pumps for various tyrosine kinases and how to use docking models to develop kinase inhibitors.

With this selection of papers we want to emphasize that with proper attention to the role of ADMET the use of the protein kinase inhibitors can be improved and extended to other applications, while for some drugs development should have been discontinued earlier. It can also be concluded that dose adaptation is sometimes necessary due to poor ADMET properties.

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