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Teaser This is a comprehensive review of the evidence for dose individualization of TKIs used for the treatment of solid tumors. Current data suggest that, for imatinib, sunitinib, pazopanib, and axitinib, treatment could be optimized by dose individualization.

Individualized dosing of tyrosine kinase inhibitors: are we there yet?

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Tyrosine kinase inhibitors (TKIs) are registered at a fixed oral dose, despite their large variability in pharmacokinetics (PK). Given that the evidence for a relation between drug exposure and treatment outcome is growing, this one-dose-fits-all approach can unintentionally lead to under- and overexposure. Dose individualization could lower this variability and thereby beneficially effect treatment outcome. In this article, we explore whether TKIs used for solid tumors meet the criteria for dose individualization. Despite limitations such as retrospective analysis, current data suggest that the following C_{trough} levels could be used: imatinib 1100 ng/ml, sunitinib when continuously dosed 37.5 ng/ml, intermittent 50 ng/ml and pazopanib 20 mg/ml. A comprehensive review of the literature also shows that prospective trials investigating the influence of dose individualization on treatment outcome are warranted.

Introduction

With the increased understanding of cancer pathophysiology, tyrosine kinases have become important targets for anticancer drug design. Tyrosine kinases activate signal-transduction pathways that are crucial for growth, activation, differentiation, and death of cells [1]. Insights into dysregulation of these pathways in cancer led to the development of TKIs. With the introduction of TKIs, a new category of rationally designed targeted anticancer agents has emerged.

Fixed dosing is usually a good option for drugs with a broad therapeutic window, small interpatient variability in exposure, and limited toxicity [2]. However, most TKIs show a large variability in their exposure (PK) and treatment outcome (pharmacodynamics; PD). Different causes for variability in PK are summarized in Fig. 1. In addition, the evidence for a relation between drug exposure and response for TKIs is growing fast [3–7]. Consequently, fixed dosing could potentially result in sub- or supratherapeutic exposure with decreased therapeutic effects in some patients or increased incidence and severity of toxicity in others.

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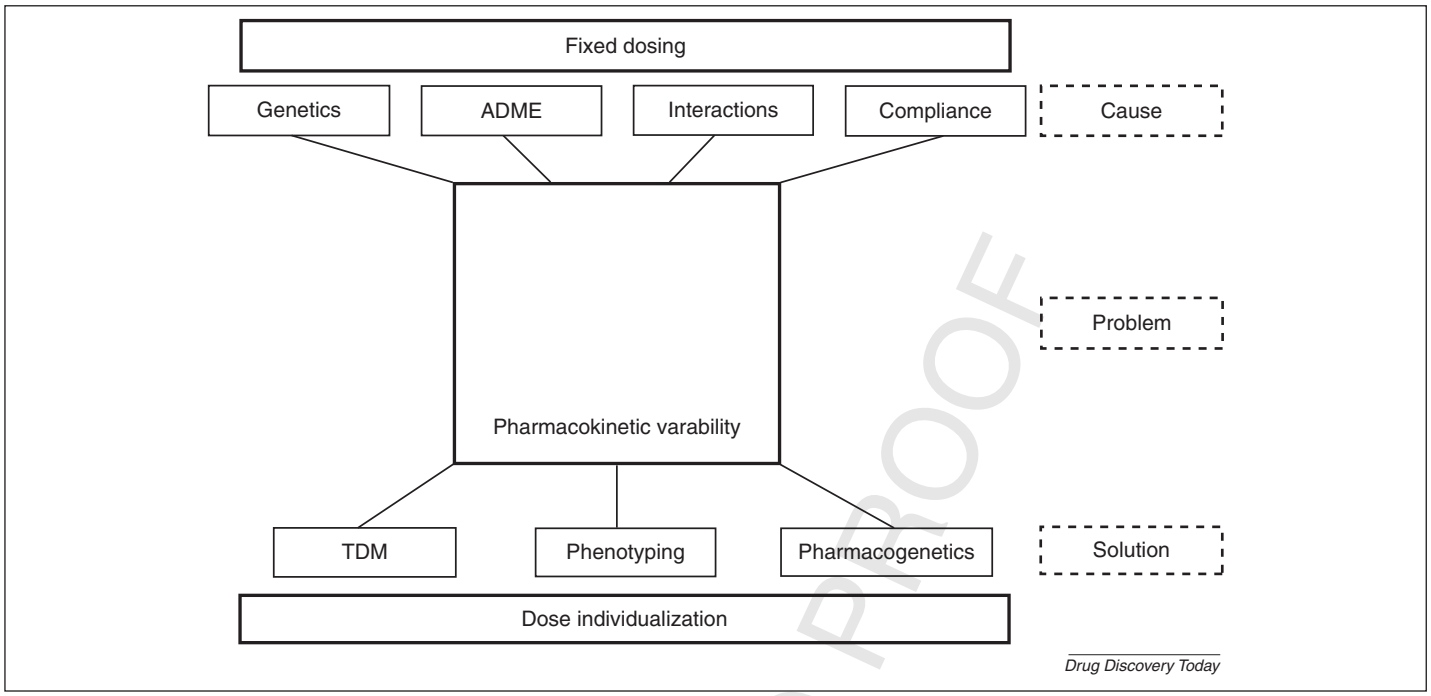

FIGURE 1

Variability of tyrosine kinase inhibitor pharmacokinetics. *Abbreviation*: ADME, absorption, distribution, metabolism, and excretion.

Several studies have focused on reducing the interpatient variability in exposure by dose individualization [8–11]. Some general criteria for dose individualization include: repeated administration, no easier assessable biomarkers to determine the response (e.g. blood pressure or rash), an available quantitative bioanalytical assay, and a validated dose-adaptation strategy. Dose proportional PK is helpful for the development of such strategies [12]. All these criteria are in general applicable to TKIs. However, the most important criteria that should be met to prove the added value of dose individualization are a narrow therapeutic window and a proven exposure–response relation [12]. A narrow therapeutic window is applicable for all anticancer agents, including TKIs. Moreover, it is important that variability in PK within patients (intrapatient) is small compared with the variability between patients (interpatient) [12]. In this review, we evaluate whether TKIs used for the treatment of solid tumors meet the criteria necessary for dose individualization. We emphasize the evidence for exposure–response relations and the inter- and intrapatient variability in PK.

Search

A PubMed search was performed using different synonyms of the keywords 'pharmacokinetics' and 'variability', and the names of the individual TKIs registered by the European Medicines Agency (EMA) up until February 2014 (Table 1). In addition, reference lists were screened for other relevant studies and registration information from the EMA and US Food and Drug Administration (FDA) was used. Results were limited to studies in humans and English full-text articles published until the 24 February 2014.

An overview of PK properties of the selected TKIs is shown in Table 2. Evidence for correlations between exposure–efficacy and exposure–toxicity is summarized in Tables 3 and 4, respectively. Table 5 describes the inter- and intrapatient variability in PK.

Axitinib

Correlation between exposure and efficacy

Recently, a study that used pooled data of 168 patients with metastatic renal cell carcinoma (mRCC) showed that patients with an area under curve $(AUC)_{0–24} \geq 300$ ng hour/ml after 4 weeks of treatment had significantly ($P = 0.003$) longer progression-free survival (PFS) and significant ($P < 0.001$) longer overall survival (OS) compared with patients with an $AUC_{0–24} < 300$ ng hour/ml [13]. Moreover, with every 100 ng hour/ml increase in $AUC_{0–24}$, a 1.5-fold increase in probability of partial response (PR) was found ($P < 0.001$) [13]. In another study, 49 patients with mRCC were grouped into four quartiles based on their day 1, 1–2 hour post-dose axitinib levels. Patients in the third quartile ($C_{1–2}$ 45.4–56.4 ng/ml and $AUC_{0–12}$ 154–620 ng hour/ml) showed the best 5-year clinical outcome with longer OS, PFS, and higher overall response rate (ORR) [14]. The better outcomes in the third quartile compared with the fourth quartile were explained by the higher incidence of grade ≥3 toxicities leading to early discontinuation and interruptions in the fourth quartile. Another pooled analysis found a median OS of 69 weeks for patients with an $AUC_{ss} \leq 605$ ng hour/ml versus 88 weeks for patients with an $AUC_{ss} > 605$ ng hour/ml, but this difference was not significant ($P > 0.05$) [15]. However, this analysis did show that patients with diastolic blood pressure (dBP) ≥ 90 mmHg had longer OS compared with patients with dBP < 90 mmHg, which was also shown in other analyses [13,16–19].

A double-blind placebo-controlled randomized phase II study prospectively evaluated the effect of axitinib dose titration on treatment outcome in 203 patients with mRCC [20]. Patients started with axitinib 5 mg twice daily (BID) for 4 weeks. Patients with BP ≤ 150/90 mmHg, no grade 3/4 axitinib-related toxicities, no dose reductions, and ≤2 antihypertensive treatments, were randomized to receive axitinib 5 mg BID plus dose titration up

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