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Opportunities and Challenges in Clinical Studies of Generic Anticancer Tyrosine Kinase Inhibitors

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PURPOSE

Tyrosine kinase inhibitors (TKIs) are multi-targeted anticancer drugs with high activity towards several families of receptor and nonreceptor tyrosine kinases involved in angiogenesis, tumor growth and metastatic progression of cancer. Many of these will be running off-patent, sequentially, in the next few years. Bioequivalence (BE) studies are needed for the development and regulatory approval of generic products of TKIs.

Biopharma Services Inc. (BPSI) has a proven track record and experience with BE studies on TKIs and other oncology drug products.

OBJECTIVES

The objectives of this work is to :

- ❑ Highlight the prominent pharmacokinetic (PK) properties of TKIs.
- ❑ Assess the variability of TKIs in BE clinical trials.
- ❑ Discuss the reasons for the high variability of some TKIs.
- ❑ Identify the safety profiles (in terms of AEs) observed in clinical trials.
- ❑ Suggest an optimized study design for BE studies of this class of drugs.

METHODS

BE studies (fast/fed) as follows:

- ❑ NHV (total =1360)
- ❑ Well-controlled standardized conditions.
- ❑ BE study design shown below:

Table (1): TKIs and Design for BE study

TKIs	Total studies	BE study Design
Axitinib	4	Single-dose (5 mg), 3-way partial-replicate
Dasatinib	9	Single dose (100 or 140 mg), 4-way fully replicate
Erlotinib	5	Single dose (150 mg), 2-way crossover
Gefitinib	2	Single dose (250 mg), 2-way crossover and 4-way fully replicate
Imatinib	10	Single dose (400 mg), 2-way crossover
Regorafenib	5	Single dose (40 mg), 2-way crossover
Sunitinib	2	Single dose (50 mg), 2-way crossover
Total = 7	**Total = 37**	

RESULTS

Oral absorption of TKIs spanned from very fast (1.3 h Tmax for dasatinib), to fast 3.5 h (Tmax for axitinib, erlotinib and regorafenib) to relatively slow absorption 6 h (gefitinib) & 8 h (sunitinib).

Under fed state, there was a slight delay in Tmax and a relatively higher variability compared to the fasting state for the same drug (results not shown).

The **inter-subject variability** can be indicated by the error bars (for SD) in the profiles below.

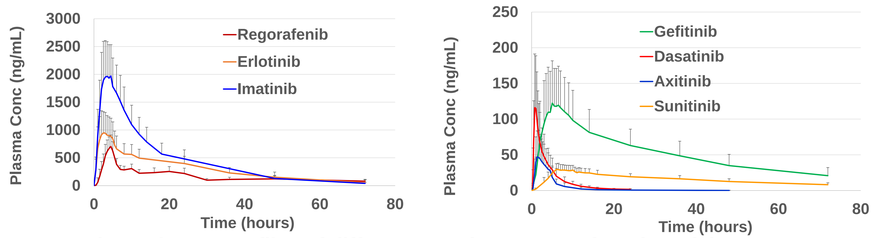

Fig 1. Plasma Profiles of different TKIs in NHV as a function of time

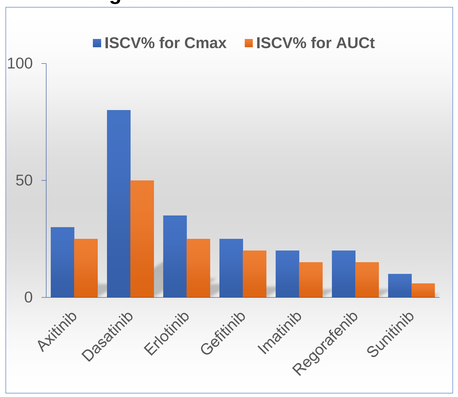

Fig 2. Intra-subject variability for different TKIs

Table (2): PK Parameters of TKIs

TKIs (dose)	No. of studies	AUC_t (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)
Axitinib (5mg)	4	220	50	2.0	6.0
Dasatinib (100 - 140 mg)	9	450	160	1.5	5.5
Erlotinib (150 mg)	5	2300	1120	2.6	15.0
Gefitinib (250 mg)	2	3600[a]	135	6.0	26.0
Imatinib (400 mg)	10	34000	2100	3.4	15.0
Regorafenib (40 mg)	5	15000[a]	750	3.5	40.0
Sunitinib (50 mg)	2	1200[a]	30	8.5	36.0

The PK parameters are the mean of studies conducted at BPSI
[a]AUC_{72} was the calculated parameter

The most common AEs were somnolence and headache. 7 subjects did not complete study due to AEs for dasatinib, and 1 subject for axitinib. The safety profile was almost the same in fasting & fed state.

Table (3): AEs reported in Studied TKIs

TKIs	# AE/Subjects	Mild	Moderate	Severe
Imatinib	220/276	204	16	0
Erlotinib	39/86	39	0	0
Dasatinib	263/250	250	10	1
Axitinib	61/102	61	0	0
Gefitinib	43/88	43	0	0
Regorafenib	70/88	70	0	0
Sunitinib	22/24	22	0	0

CONCLUSIONS

- ❑ The studied TKIs exhibited different PK profiles and plasma exposure.
- ❑ The variability of TKIs was shown to be diverse: ranging from high (dasatinib), medium (axitinib, erlotinib, gefitinib, regorafenib, imatinib) to very low (sunitinib).

Challenges:

Potential reasons for the variability could be one /more of:

- High variability esp. for the reference product → dasatinib.
- Drug polymorphism → axitinib (with impact dissolution and hence absorption)
- BCS Class **II** / solubility problems → all TKIs are BCS Class **II** (except sunitinib Class **III**).
  For Class II drugs inadequate and pH-dependent dissolution contributes to the variability in absorption.
- Variable exposure due to fat content in meal → regorafenib.
  Depending on fat content in meal, a higher and lower exposure after low-fat meal and high-fat meal, respectively than the fasting state).
- CYP2D6 metabolism → gefitinib.
  Poor vs extensive metabolizers resulted in variable exposure and/or carryover effect).

Opportunities:

- While the FDA specific-guidance suggests BE studies in patients, yet BPSI conducted in NHV (total of 1360 subjects under Principal investigator as per GCP) and there were no major safety issues.
- Overall, the TKIs were well tolerated by NHV.
- Despite the variability, an optimized fully-replicate design with the scaled- approach could be used with sufficient sample size.
- A well-controlled standardized study is needed to reduce variability.

Recommendations:

- Our experience with TKIs tells that due to difference in TKIs variability, the study design for BE studies would be either a simple crossover to more complicated fully replicate design.

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