Cachexia-associated anticancer drug toxicity is minimally mediated by alteration of drug's pharmacokinetics: Erlotinib as case study

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Background and objective

- **Cachexia:** is an irreversible condition of muscle mass loss characterised by chronic systemic inflammation and energy imbalance
- It commonly occurs in cancer patients, and impacts their response to treatment and survival [1,2]
- Toxicity of different anticancer agents, and in different cancer types has been associated with cachexia-related muscle mass loss [3–8]
- *Underlying mechanism to this observed toxicity remains unclear*
- **Erlotinib**, is a tyrosine kinase inhibitor widely used for the treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer

Our hypothesis: toxicity is mediated by a potential impact of cachexia-related muscle mass loss on the pharmacokinetics (PK) of anticancer drugs

Objective

- Explore impact of skeletal muscle on the PK parameters of erlotinib and its metabolite (OSI-420) to identify, if change in body composition, represented by muscle mass loss, alters drug PK and exposure, and subsequently elevates drug concentration leading to toxicity

Methods

Study design

Clinical trial: NCT01402089 [9]

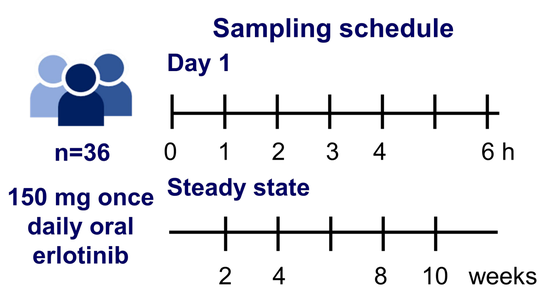


Fig 1 Study design and sampling schedule

- 36 patients with advanced inoperable NSCLC
- Samples collected at baseline, on day 1 and at steady state **(Fig 1)**
- Plasma erlotinib and OSI-420 were analysed using a validated LC-MS/MS method [9]

Baseline skeletal muscle measurement

Skeletal muscle area (SMA)

- Measured at the 3rd lumbar vertebrae (L3) using computed tomography. Images analysed and converted to area using Slice-O-Matic software
- Linearly correlates with whole-body composition [10]

Skeletal muscle volume (SMV) [11]

$$SMV(L) = 0.166 L/cm^2 \cdot \mathrm{SMA}(cm^2) + 2.142\ L$$

Skeletal muscle mass (SMM) [12]

$$SMM(kg) = SMV(L) \cdot 1.06\ g/cm^3$$

Erlotinib and OSI-420 PK model [9]

- Adopted as base model **(Fig 2)**
- Absorption rate constant (K_a) fixed to 1.09 h^{-1} [13]

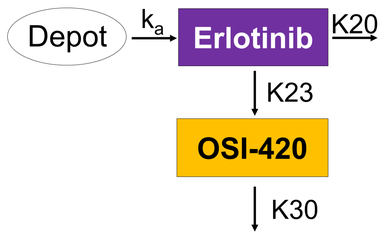
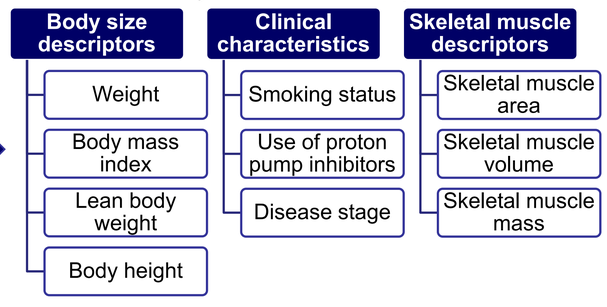


Fig 2 Schematic diagram of PK model of erlotinib and its metabolite (OSI-420). K_a: absorption rate constant. K20: elimination rate constant from parent compartment. K23: rate constant from parent compartment to metabolite compartment. K30: elimination rate constant from metabolite compartment.

Sub-population, model robustness, and covariate analysis

- Skeletal muscle measurements available for only a subset of patients (n=23)
  - ➢ Confirm PK model robustness for the sub-population
  - ➢ Assess potential impact of

… on erlotinib and OSI-420 PK parameters



Results

Sub-population

- Distribution of patients characteristics in the full population was retained in the sub-population **(Fig 3)**

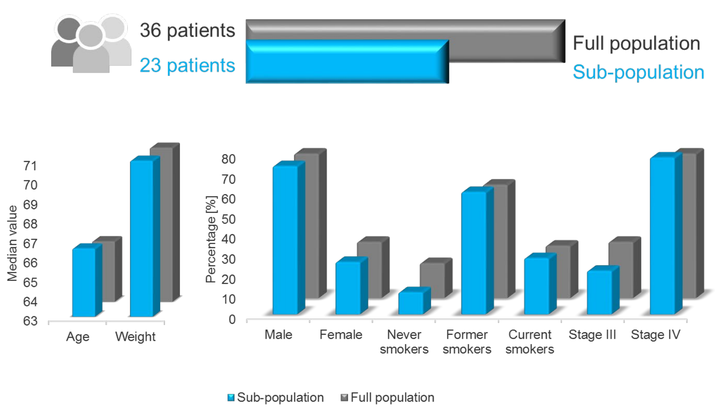


Fig 3 Distribution of the full and sub-population main characteristics

PK model robustness

- Relative percent change on population estimates:
  - Structural parameters: -0.374%–26.0%
  - Interindividual variability: -45.1%–5.065%
- GOF plots and VPC:
  - No misspecifications **(Fig 4,5)**

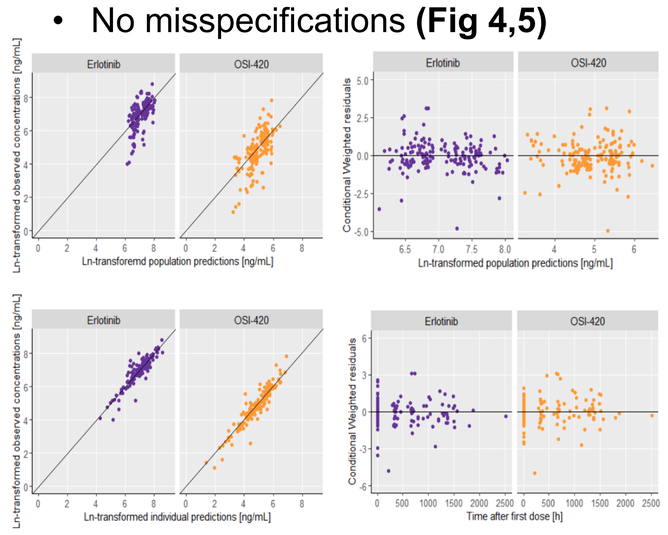


Fig 4 GOF plots of erlotinib (purple) and OSI-420 (orange)

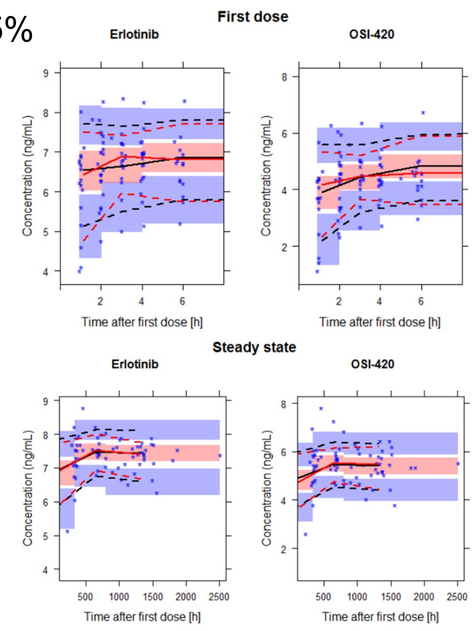


Fig 5 VPC of erlotinib and OSI-420 model (n=200). Dots: measured concentrations. Lines: 10th, 90th percentile (dashed), 50th percentile (solid) of the observed (red) and simulated (black) concentrations. Shaded areas: 95% confidence interval of the simulated percentiles. Number of bins: 5 with equal number of observations.

Covariate analysis

- Different skeletal muscle descriptors
- Body size descriptors
- Clinical characteristics

} Did not influence CL or V of erlotinib or OSI-420

Observed differences in muscle mass did not impact the distribution and exposure of erlotinib.

Discussion and Conclusion

- **Lack of association** between skeletal muscle loss and erlotinib PK
- Cachexia-associated alteration in drug exposure and toxicity possibly mediated through a **non-PK pathway.** Toxicity is probably influenced by the systemic inflammatory status induced by cachexia or co-morbid condition of the patient

Next steps

- Muscle mass impact on the PK of **other anticancer drugs** in advanced cancer patients will be investigated to explore if specific **drug properties** (e.g. physicochemical) alter drug PK and/or exposure in response to skeletal muscle loss.

References

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