Extended Abstract

Pharmacometrics and systems biology in oncology: Is there an intersection?

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Key words
pharmacometrics
– systems biology – monoclonal antibodies
– biomarkers – systems pharmacology

Background

Oncology involves a therapeutic area with complex and individual disease states and disease progression and there is a limited number of anticancer drugs available. The drugs are usually administered in empirical complex dosing regimens which result in highly variable success rates. The following two approaches to achieve a more streamlined and rational drug development and drug treatment seem appealing:

1. More sophisticated understanding of the patient’s health/disease state and disease progression (“system”).
2. Development of new drugs with defined and tailored treatment regimens.

The fundamental challenge of anticancer drug treatment is to effectively eliminate cancer cells in an individual patient using a treatment protocol with dosing regimens that are tolerated. Most classical cytotoxic anticancer agents do not distinguish between healthy and cancer cells and thus inhibit essential functions in both healthy and malignant cell populations. A new generation of anticancer drugs has been designed to interfere with specific molecular targets identified as playing a critical role in tumor growth and progression. In both cases, elucidation of the mechanisms and pathways at the molecular, cellular, tissue, organ and organism level is crucial. There is an urgent need for markers that indicate success, failure or toxicity prior to or at an early stage of the anticancer treatment (“biomarkers”).

Methodology and concepts

Pharmacometrics represents an emerging science based on a transdisciplinary approach bridging concepts of biology, pharmacology, clinical pharmacy and pharmacology, mathematics and statistics: Pharmacokinetic/pharmacodynamic/biomarker/disease modeling aims to elucidate the mechanism-based relationships between dosing – drug exposure – resulting drug effects while incorporating knowledge of the patients and their disease [1].

Systems biology aims from a bottom-up approach to model important system properties to understand the complex pathways, networks and regulatory and feedback mechanisms on different spatial and temporal levels [2].

Due to their attractive characteristics (e.g. high specificity to target, i.e., binding (only) to specific disease-associated structures), monoclonal antibodies (mAbs) present an innovative class of biopharmaceuticals with increasing clinical importance. However, in some cases only a certain fraction of patients benefits from these “targeted therapies” [3]. In addition, in therapeutic use the outcome with respect to efficacy and toxicity (incl. immunogenicity) has been reported to be considerably variable suggesting mechanisms inherent to patient (system) characteristics.

For two mAbs targeting the epidermal growth factor receptor (EGFR) system, cetuximab and panitumumab, metastatic colorectal tumor patients bearing the mutated K-ras gene did not benefit (progression-free and overall survival) from the drug treatment [4]. The mAb trastuzumab has been approved in patients with metastatic breast cancer but being indicated only in those ~ 25 – 30% of patients with relative overexpression of the HER2/neu receptor on the cell surface of the tumor cell. For these mAbs, the biomarkers K-ras and HER2 represent the status of the patient or the state of disease. In their static use as ‘exclusion’ criterion, these biomarkers serve as a diagnostic tool and prevent useless or even harmful treatments for patients. In that, bio-
markers nowadays present an enormous value in stratified (not personalized) medicine.

Additionally, the pharmacokinetics (PK) of mAbs is unique compared to small molecule drugs: their binding/elimation characteristics comprise multiple pathways, in particular the often observed parallel linear and nonlinear elimination pathways [5]. Furthermore, PK is also influenced by the pharmacodynamics (PD) and vice versa in terms of binding to the target (“target-mediated drug disposition”, TMDD). Moreover, intracellular downstream processes of the drug-receptor complex should be taken into account [6]. Several PK and PD parameters have been reported to be related to patient demographic characteristics, e.g., the different clearances to body size [5]. However, systematic and mechanic investigations are still sparse but highly warranted.

**Perspectives**

Both disciplines – pharmacometrics and systems biology – are rather young, have internationally gained attractiveness but have up-to-now often been considered only separately. Especially in oncology, it is time to revisit the current approaches of data generation and of data analysis incl. modeling & simulation concepts. One objective in joint efforts could result in a thorough understanding of the underlying mechanisms of drug disposition, target binding, drug-target complex signal transduction, e.g. inside the cell in various sub-cellular compartments and target dynamics, as well as the impact of patient, treatment and study characteristics. To one end, biomarkers might extend their role from being used today in stratified medicine based on target (non)expression to serving in future as mechanism-driven, predictive biomarkers for personalized medicine.

As a prerequisite, the strengths of basic and applied research groups have to be combined by exploiting the wealth of

- Multiple levels of data, namely
  1. molecular level
  2. cell level
  3. tissue level
  4. organ level
  5. patient level (→ society)

and

- Multiple types of data (quantitative, over time), namely
  1. target expression
  2. key pathway markers
  3. drug concentrations
  4. biomarker/PD data
  5. pharmacogenetic data
  6. clinical data

What is lacking today is not only the “network of experimental, in silico and clinical data” but also the “network of methodological expertise”.

In future, effective integration of both disciplines – pharmacometrics and systems biology as systems pharmacology – might not only foster research on pharmacokinetics, pharmacodynamics and biomarkers for disease and treatment outcome. Combining approaches of cross-disciplinary interaction (e.g. preclinical and clinical oncology) requiring open mindedness and communication might also streamline decision making in the two important fields:

1. in drug development (known as: model-based drug development) and
2. in patient care to increase the benefit/risk ratio of the therapeutic use in the individual tumor patient (proposed to be named as: model-based patient care).

**References**


