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Review

Application of pharmacometrics and quantitative systems pharmacology to cancer therapy: The example of luminal a breast cancer

Brett Fleisher[a], Ashley N. Brown[b], Sihem Ait-Oudhia[a,*]

[a] Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, 6550 Sanger Road, Room #469, Orlando, FL, 32827, USA
[b] Institute for Therapeutic Innovation, Department of Medicine, University of Florida, 6550 Sanger Road, Orlando, FL, 32827, USA

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ABSTRACT

Breast cancer (BC) is the most common cancer in women, and the second most frequent cause of cancer-related deaths in women worldwide. It is a heterogeneous disease composed of multiple subtypes with distinct morphologies and clinical implications. Quantitative systems pharmacology (QSP) is an emerging discipline bridging systems biology with pharmacokinetics (PK) and pharmacodynamics (PD) leveraging the systematic understanding of drugs' efficacy and toxicity. Despite numerous challenges in applying computational methodologies for QSP and mechanism-based PK/PD models to biological, physiological, and pharmacological data, bridging these disciplines has the potential to enhance our understanding of complex disease systems such as BC. In QSP/PK/PD models, various sources of data are combined including large, multi-scale experimental data such as −omics (i.e. genomics, transcriptomics, proteomics, and metabolomics), biomarkers (circulating and bound), PK, and PD endpoints. This offers a means for a translational application from pre-clinical mathematical models to patients, bridging the bench to bedside paradigm. Not only can these models be applied to inform and advance BC drug development, but they also could aid in optimizing combination therapies and rational dosing regimens for BC patients. Here, we review the current literature pertaining to the application of QSP and pharmacometrics-based pharmacotherapy in BC including bottom-up and top-down modeling approaches. Bottom-up modeling approaches employ mechanistic signal transduction pathways to predict the behavior of a biological system. The ones that are addressed in this review include signal transduction and homeostatic feedback modeling approaches. Alternatively, top-down modeling techniques are bioinformatics reconstruction techniques that infer static connections between molecules that make up a biological network and include (1) Bayesian networks, (2) co-expression networks, and (3) module-based approaches. This review also addresses novel techniques which utilize the principles of systems biology, synthetic lethality and tumor priming, both of which are discussed in relationship to novel drug targets and existing BC therapies. By utilizing QSP approaches, clinicians may develop a platform for improved dose individualization for subpopulation of BC patients, strengthen rationale in treatment designs, and explore mechanism elucidation for improving future treatments in BC medicine.

Abbreviations: AI, Aromatase Inhibitors; ASCO, American Society of Clinical Oncology; BC, Breast cancer; cMLV, cross-linked multilamellar liposomal vehicle; CSC, Cancer Stem Cells; ePD, Enhanced pharmacodynamic; EMT, Epithelial-mesenchymal transition; ER, Estrogen Receptor; ET, Endocrine therapy; GWAS, Genome-wide association studies; HER2, Human Epidermal growth factor Receptor 2; HR^+, Hormone Receptor positive; LDT, Laboratory Developed Test; LABC, Luminal A breast cancer; MET, Mesenchymal-epithelial transition; PD, Pharmacodynamics; PK, Pharmacokinetics; PMX, Pharmacometrics; PBPK, physiologically-based PK; PM, poor metabolizer; PR, Progesterone Receptor; PTMs, Post-translation modifications; SERD, Selective Estrogen Receptor Down-regulator; SERM, Selective Estrogen Receptor Modulators; SPNs, Survival Prognostic subNetwork signatures; TCGA, The Cancer Genome Atlas; TIMMA, Target Inhibition interference using Maximization and Minimization Averaging; TF, transcription factors; WGCNA, Weighted gene co-expression network analysis.

* Corresponding author.
E-mail address: sihem.bihorel@cop.ufl.edu (S. Ait-Oudhia).

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Contents

1. Introduction

More than 246,000 women were diagnosed with breast cancer (BC) in the year 2016 and 40,400 women are expected to succumb to the disease this year [1]. The time is now for a radical refocus in mindset to revolutionize treatment for this disease in effort to reduce these statistics.

BC is a complex disease, comprised of cells, each with its own origin, etiology and fate, connected by convoluted signaling pathways encompassed in a sustaining microenvironment. Classification of BC is complex and is not a pure stratification [2,3]. Nonetheless, breast tumors are tested for the presence of receptors, including the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). The outcomes of these tests result in the classification tree depicted in Fig. 1 and help clinicians individualize treatment. Despite this primary stratification, variability in treatment outcomes remains vast, due to the complexity and heterogeneity of the disease as well as the patient. Luminal A breast cancer (LABC) in a subset of BC that is hormone receptor positive (HR^+) and HER2 negative ($HER2^-$) [4]. It represents 40% of all BC subtypes [5] and is associated with a time-dependent mortality rate: short–term prognosis is favorable with positive bias disappearing over time and eventually reversing [6]. Anti-cancer treatments for patients with LABC are often non-specific, and consequently, adverse events experienced by these patients can be limiting [7,8]. Regimented individualized therapy in LABC extends only as far as profiling the patient's BC subtype and assigning the appropriate treatment as per the guidelines and the attending clinical team's opinion. For LABC, targeted therapy is becoming the modern angle of chemotherapy [9], partially because of the continuous increasing trend of resistance of LABC to endocrine therapy (ET) [10,11]. While recent pharmacological approaches such as synthetic lethality [12] and tumor priming [13] – both will be discussed later in this review article- allow for optimization of combination therapy strategies, targeted therapies exploit the differences between normal cells and cancerous cells by pursuing these differences and selectively eradicating the cancer cells, allowing for specific and optimized therapy of the cancer. Personalized medicine and targeted therapy have significantly evolved over the last few decades, but there are opportunities for improvement to decrease toxicities and recurrence. This could be achieved through the application of QSP approaches with a deeper understanding of LABC systems biology. In other words, the selection of eligible patients for targeted therapy is multifaceted, adverse event profiles are significant, and dosing is open to discussion. The thesis of this paper is that with the right tools, interdisciplinary collaboration, and creative minds, treatment could become more precise and effective.

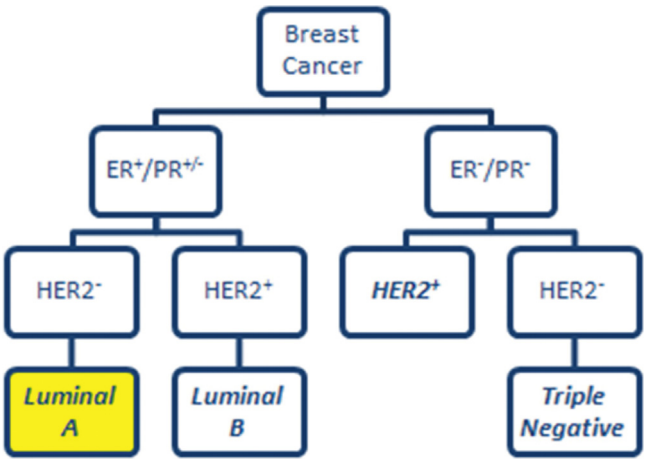

Fig. 1. Stratification of breast cancer (BC) subtypes according to the expression on cancer cells of three membrane receptors: estrogen receptors (ER), progesterone receptors (PR), and Human Epidermal growth factor Receptor 2 (HER2). Luminal A subtype is highlighted in yellow as it is the focus in this review article.

The study of PK and PD has long been incorporated in drug development to aid in dose discernment. PK is known as what the body does to the drug, describing the time-course of exposure through factors influencing absorption, distribution, metabolism and excre-