Chapter 3
Cancer Drug Delivery: Pharmacogenetics, Biomarkers, and Targeted Therapies

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ABSTRACT

Advancements in cancer drug delivery have led to the development of personalized oncology care through molecularly-driven targeted therapies. Understanding molecular and cellular mechanisms which drive tumor progression and resistance is critical in managing new treatment strategies which have shifted from empiric to biomarker-directed therapy selection. Biomarker-directed therapies have improved clinical outcomes in multiple malignancies as monotherapy and in combination with other treatment modalities, however the changing scope of treatment options presents new opportunities and challenges for research. Furthermore, pharmacogenetics may provide a rationale method of personalizing anticancer drug dosing and supportive care management for oncology patients. This chapter reviews biomarker classifications and pharmacogenetics in anticancer therapy and supportive care. Examples of biomarker-directed therapies and clinical assays, in addition to future directions of molecular profiling in oncology therapy management are discussed.

INTRODUCTION

Novel methods of individualizing cancer drug delivery and selection are critical to improve patient outcomes given the large heterogeneity in drug response that exists across the cancer patient population. Until recently, the majority of genomic cancer research has been in discovery and validation; however, as our knowledge of tumor molecular profiling improves, the implementation of genomic cancer medicine in the clinic becomes increasingly tangible, paralleled with the development of dozens of targeted cancer therapies (Tran et al., 2012). Our current understanding of cancer at the molecular level has resulted in a shift from characterizing tumors solely based on their anatomical location and histology to consideration

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of their molecular profile, opening an array of possibilities for a targeted approach to cancer therapy (Macconaill, Van Hummelen, Meyerson, & Hahn, 2011).

Pharmacogenetic biomarkers found within the tumor and the host offer valuable information for personalizing anticancer drug delivery. As the number of clinical assays available to test for pharmacogenetic biomarkers increases, it is imperative for clinicians to understand the therapeutic implications of mutations occurring within these molecular pathways to aid in drug selection and delivery. This chapter aims to summarize clinically relevant pharmacogenetic biomarkers, which may be used to personalize cancer therapy selection and dosing, in addition to a review of pharmacogenetics in supportive care management related to the treatment of cancer-related symptoms. Tables 1 and 2 summarize clinically relevant somatic and germ-line pharmacogenetic biomarkers and drug targets, and their respective clinical assays available in practice.

BACKGROUND: BIOMARKERS OVERVIEW

DNA analysis for pharmacogenetic purposes can be performed with either somatic or germ-line DNA. The major difference between somatic and germ-line DNA is the origin of the mutated cell (Patel, Mandock, & McLeod, 2014). While germ-line DNA is found in germ cells (sperm or egg) and therefore inherited and transmitted to the offspring, somatic DNA is found within the tumor after conception and subsequently not passed on to offspring, i.e. acquired after birth. Germ-line DNA is readily obtained by blood samples, and variations, if present, will occur homogenously throughout any randomly drawn blood sample within the same individual. Somatic DNA must be obtained by tumor biopsy and is therefore subject to sample selection. Common practice is to obtain one biopsy from the primary tumor for molecular analysis, as it was assumed that tumors were homogenous and the section sampled accurately represented the complete tumor composition. However, there is evidence to suggest that intra-tumor heterogeneity exists within cancer, where molecular analysis of one biopsy site may differ from another biopsy site (Gerlinger et al., 2012). Additionally, somatic mutations may change or evolve during cancer progression, resulting in a significant challenge in applying routine cancer pharmacogenetics to the clinic. While germ-line DNA is particularly useful for determining the pharmacokinetic behavior of a drug by understanding variations in drug metabolizing enzymes and/or transporters, somatic DNA is particularly useful in determining the pharmacodynamic effect of a drug and ultimately tumor response (Deenen, Cats, Beijnen, & Schellens, 2011).

Cancer biomarkers can be broadly categorized into two classifications: prognostic and predictive. A prognostic biomarker is mainly associated with disease outcome in the absence of treatment (i.e. Oncotype Dx, Mammaprint), while a predictive biomarker is valuable in assessing drug response (i.e. *ALK* [anaplastic lymphoma kinase], *BCR-ABL*, *EGFR* [epidermal growth factor receptor] (Mandrekar & Sargent, 2009; Patel, 2014).

Alternatively, some biomarkers may be classified as both prognostic and predictive (i.e. human epidermal growth factor receptor-2 [*HER2*], KRAS [Kirsten rat sarcoma viral oncogene homolog], and *BRAF* [v-RAF murine sarcoma viral oncogene homolog B]). Figure 1 highlights several strategic growth pathways, which cancer cells can activate through somatic mutations, and their respective targeted therapies. Pharmacodynamic biomarkers, a subset of predictive biomarkers, are useful in measuring the treatment effects of a drug on the tumor or on the host and can be used to guide dose selection; examples include dihydropyrimidine dehydrogenase (*DPYD*), thiopurine-S-methyltransferase (*TPMT*) and uridine diphosphate glucuronosyl transferase 1A1 (*UGT1A1*) amongst others (Patel, 2014; Sawyers, 2008).