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Approaches to the discovery of pharmacogenomic markers in oncology: 2000–2010–2020

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Abstract

Pharmacogenomics is emerging as an important component both in facilitating new drug development and in improving the utility of existing chemotherapeutic agents. Both candidate gene and genome-wide approaches have been used to identify genetic markers associated with chemotherapeutic response and/or toxicity. New molecular targeted agents have been designed based on a sophisticated understanding of the molecular alterations defining cancers. Over the next decade, the translation of these findings into clinical practice, as well as functional studies of genetic variants, is likely to take center stage. More comprehensive evaluation of the human genome, including the examination of rare SNPs, copy number variations, tandem repeats and epigenetic effects, will further improve our understanding of the relationship between genetics and drug response.

Keywords

cancer; chemotherapy; genome-wide association study; pharmacogenomics

The paradigm of individualized drug therapy based on a person's unique genetic make-up is especially desirable in the field of oncology, where the therapeutic index is often narrow and the consequences of drug toxicity can be life threatening. Generally, anticancer agents are administered at the maximally tolerated dose, as defined for a large population, with an expectation that approximately a third of patients will have unacceptable toxicity. Polymorphisms that affect drug clearance often lead to recognizable clinical events, such as myelosuppression or neurotoxicity. Thus, if clinicians could better predict which individuals are at the greatest risk of suffering chemotherapy-related toxicities, then the overall care of cancer patients could be greatly impacted with patient-specific dose modifications, optimization of treatment choice (when several equivalent therapies exist), or avoidance of a therapy when toxicity risks outweigh potential benefits. More important is the ability to predict

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those patients at greatest risk for nonresponse to specific treatment, as modifying their therapeutic regimen could be highly beneficial. This commentary will focus on the methods used to identify genetic variants that have been important in chemotherapy over the past decade and expected changes over the next decade.

Past

Improving cancer patient care through our understanding of the pharmacogenomics of response and toxicity of existing chemotherapy is critical; however, many existing agents are not effective and new agents are needed. Over the past decade, a number of molecularly targeted agents have been discovered based on a more sophisticated understanding of genetic and molecular processes within cancers. Examples of agents developed include trastuzumab (Herceptin[®], Genentech, CA, USA), a Her-2 inhibitor, designed to target the amplified Her-2 receptors on the breast cancer cell surface [1]; imatinib (Gleevec[®], Novartis, Basel, Switzerland), targeting abnormal Bcr–Abl fusion protein in chronic myeloid leukemia [2]; and a series of EGF receptor-tyrosine kinase inhibitors [3] and anti-VEGF agents [4]. Furthermore, increased knowledge in epigenetics has led to the development of novel histone deacetylase inhibitors and DNA methylation inhibitors [5]. Figure 1A illustrates the US FDA approval time for various chemotherapeutic agents over the past decade. Although cytotoxic agents will continue to play a significant role in cancer treatment over the next decade, targeted agents will continue to be developed and are likely to become central players in clinical cancer management.

To see where approaches in the pharmacogenomics of anticancer agents are headed, it is instructive to take a step back and see how approaches emerged from the pre- to post-genomic era. In the early 2000s and for the previous decades, the approach to studying genetic variants important in response to chemotherapeutic agents was primarily via a candidate gene or pathway centric approach, a method that makes assumptions about which genes are most important in the drug's activity. Observations (e.g., severe toxicity) were made in patients following treatment with oncology drugs, and case–control studies were then designed to evaluate genetic variations contributing to the observed effect. Follow-up functional studies were often performed in cultured cells or animal models. Most of these studies involved a genetic variant within a drug-metabolizing gene that had a large effect on the degree or rate at which a drug was converted to its metabolites. Examples include: genetic variations in *TPMT* that account for more than 90% of cases with low or intermediate TPMT enzyme activity and lead to an increased risk for severe myelosuppression after 6-mercaptopurine treatment [6]; *UGT1A1**28, which is associated with a decrease in UGT1A1 expression and an increased risk of severe neutropenia when medium- or high-dose irinotecan is administered [7]; and lack of response to tamoxifen in *CYP2D6* poor metabolizers [8]. With the success of these single gene pharmacogenetic discoveries, additional prognostic tools to help guide chemotherapy based on an individual's somatic or germline genetic profile have been developed (Figure 1B).

Present

Current approaches used to identify genetic variants contributing to response or toxicity associated with chemotherapy have been driven, to a greater extent, by technology that now allows us to evaluate the entire genome. This is very useful because such studies are unbiased, take into account pharmacodynamic and pharmacokinetic genes, and consider that drug response is multigenic with many genes contributing smaller effects. In contrast to the candidate gene approach, which is hypothesis driven, genome-wide approaches are considered to be hypothesis generating. However, the genome-wide approach can result in false discoveries due to multiple testing, and requires large sample sizes for reasonable power to detect associations. In oncology, replication studies are particularly challenging because the

study requires individuals with the same cancer, treated in the same manner in a field where the standard of care tends to change as new therapies are tested. For these reasons and the challenges of discovery studies in humans, some have turned to cell lines. These cell-based models have shown that chemotherapeutic-induced cytotoxicity is heritable [9,10] and amenable to genetic dissection [9,10]. The utility of these cell-based models will certainly be better understood over the next decade.

Since the declared completion of the human genome sequence [11] and the comprehensive genomic characterization of human cancers [12], genome-wide association studies have gained popularity. Numerous studies employed gene-expression arrays to identify signatures that classify subtypes of various cancers [13–15] and subgroups with differential sensitivity to chemotherapeutic agents [16,17]. In addition to expression signatures, genetic signatures, in the form of SNPs [18,19], copy number variations [20,21] and mutations [14], are coming to the forefront as a means to identify individuals that are likely to respond to chemotherapy. Although scientists have enjoyed a rapid advance in technology, translating laboratory findings into the clinic has been painfully slow. This is owing to the difficulty in conducting large prospective pharmacogenomic and/or pharmacoeconomic trials to demonstrate the scientific value and cost-effectiveness of pharmacogenomic prediction models. This is particularly true in the field of oncology.

Future

What will the next decade bring us in terms of genetic information? Surprisingly, the Human Genome Project demonstrated that only 2% of the human genome is actually genes [11]. Therefore, researchers have begun to move beyond the scope of genes and into the regulatory sequence and the study of noncoding sequences. Intergenic, intronic and other noncoding regions may harbor regulators of gene expression [22]. Meanwhile, experimental tools have included microsomes, hepatocytes and HapMap lymphoblastoid cell lines rich in genetic information [23]. Over the next decade, researchers are likely to make the transition from large genome-wide association studies to a combination of genome-wide association studies and candidate gene studies, as well as validation of true positives. There will be more genetic information, in the form of rare SNPs from the 1000 Genomes Project, copy number variations and epigenetics, that will allow a better view of contributions to phenotypic variation, but which will require clever data analysis. Certainly, over the next decade we will have a much better understanding of how genetics plays a role in differences in response/toxicity to anticancer agents in individuals from different geographic locations.

While the challenges both for oncologist/hematologist and society are significant, increasing knowledge regarding the human genome and cancer genome will be concomitant with the development of comprehensive, cost-efficient and high-throughput technologies. There will certainly be an increase in powerful tools in biomedical and clinical informatics for analyzing and storing vast amounts of data, which will enable continued growth in the field of personalized therapeutics for cancer patients. For pharmacogenomics to be successful in the field of oncology, there needs to be alternative therapies with different mechanisms available for patients whose genetics show that they are at risk for severe toxicity or nonresponse with standard chemotherapy. We expect to see more ‘designer drugs’ that are tailored to individual needs by the year 2020, along with prognostic prediction tools that can be used to guide cancer therapy.

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Figure 1. Timeline of pharmacogenetic prognostic tools and drug development from 2000 to 2020 (A) Time of approval of various cancer therapies based on US FDA approval time. (B) Timeline to show the establishment of pharmacogenetic prognostic tools. DMET: Drug-metabolizing enzymes and transporters; HDAC: Histone deacetylase.