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The Impact of Pharmacogenomics on Chemotherapeutic Drug Development and Use

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Abstract
Cancer therapy is largely dependent on general treatment guidelines, and patients undergoing chemotherapy often experience treatment failure with standard drugs. The development of individualized drug therapy through pharmacogenomics has the potential to enhance chemotherapy regimen selection and improve patient outcomes. Antineoplastic agents such as cetuximab and trastuzumab are effective in treating cancers possessing specific genetic biomarker characteristics. Patients need to undergo genetic testing before these agents are administered to ensure appropriate use. Cetuximab has been shown to improve outcomes in metastatic colorectal cancers and head and neck squamous cell carcinomas positive for EGFR. Trastuzumab has shown benefit in human epidermal growth factor receptor 2 (HER2) overexpressing cancers affecting the breast tissue and gastrointestinal tract. High costs associated with the development of targeted drugs and a lack of clinical studies exploring the effects genetic variations can have on drug therapy limit implementation of pharmacogenomics into routine practice. As drug therapy experts, pharmacists need to be aware of advances in the field of pharmacogenomics and facilitate the use of this new class of personalized drugs.

Introduction
Patients diagnosed with cancer are treated on the basis of standard drug therapy and dosing guidelines. Many factors, such as body weight, age and medical history, may also be considered in choosing a medication regimen. Despite these considerations, a patient’s response to drug therapy cannot be predicted using current methods and practice guidelines. This could translate into repeat visits to the oncologist for gastrointestinal tract. High costs associated with the development of targeted drugs and a lack of clinical studies exploring the effects genetic variations can have on drug therapy limit implementation of pharmacogenomics into routine practice. As drug therapy experts, pharmacists need to be aware of advances in the field of pharmacogenomics and facilitate the use of this new class of personalized drugs.

Cetuximab
Cetuximab (Erbitux®) is a recombinant chimeric IgG1 antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR)-1. EGFR is responsible for the growth and differentiation of epithelial cells. When epidermal growth factor (EGF) binds to the extracellular domain of EGFR, receptor dimerization occurs and intracellular protein tyrosine kinases are activated. Following kinase activation, various signaling pathways are stimulated, such as RAS-RAF-mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K-AKT) pathways. Once activated, these pathways’ signals can regulate cell proliferation, differentiation and survival. Cetuximab binds to the extracellular domain of EGFR with high affinity and competitively inhibits ligands from binding to the receptor. This leads to inhibition of phosphorylation of intracellular protein tyrosine kinases and prevents the activation of the downstream signaling pathways, resulting in the inhibition of cell growth and proliferation, ultimately inhibiting tumor growth (Figure 2).

Cetuximab was the first EGFR inhibitor approved for the treatment of metastatic colorectal cancer (mCRC). It is used as monotherapy in the treatment of EGFR-positive mCRC in patients who cannot tolerate traditional irinotecan-based therapy or in combination with irinotecan in patients who did not respond to oxaliplatin, irinotecan and 5-fluorouracil (5-FU). Traditional therapy in the treatment of mCRC includes a combination of 5-FU or capcitabine, with either oxaliplatin or irinotecan. Using cetuximab in combination with 5-FU and irinotecan or oxaliplatin has been shown to improve outcomes in the first- and second-line setting of mCRC.

Cetuximab can improve overall survival when used in combination with radiation therapy in the treatment of locally or regionally advanced head and neck squamous cell carcinoma (HNSCC). It is used as a monotherapy agent in patients with metastatic or recurrent HNSCC. These patients do not typically respond to platinum-based chemotherapy. Cetuximab...
has also been shown to improve survival when used in combination with cisplatin-based chemotherapy, as compared to cisplatin alone.4

**KRAS Mutation**

RAS proteins are involved in the EGFR signaling pathways that ultimately result in cell proliferation, differentiation and survival. The three human RAS genes—HRAS, KRAS and NRAS—are involved in the pathogenesis of tumors through cell proliferation, angiogenesis and anti-apoptosis pathways.3 RAS proteins are small GTP-GDP-binding proteins which act as self-inactivating signal transducers cycling from the GDP-to GTP-bound states as a result of EGF binding to the EGFR. These oncogenic RAS proteins have reduced GTPase activity which results in an abundance of RAS proteins in the GTP-bound active state due to an inability to cycle back to the GDP-bound inactive state. This results in further activation of the downstream signaling pathways promoting cancer cell proliferation, angiogenesis and resistance to apoptosis. Mutations in the coding region of the KRAS gene lead to a constitutively active gene, which is not dependent on upstream activation of the EGFR. Cetuximab prevents the downstream cell signaling pathways from occurring by blocking EGF from binding the EGFR. Because EGFR activation results in KRAS protein activation, mutations in the coding region of the KRAS gene lead to a constitutively active KRAS gene. This mutated KRAS gene is not dependent on the upstream signaling pathways.5

**Figure 2: Cetuximab and its effects on the EGF pathway.**

A randomized trial completed by the National Cancer Institute of Canada Clinical Trials Group with the Australasian Gastro-Intestinal Trials Group demonstrated that patients harboring KRAS mutations had reduced response rates to cetuximab therapy, compared to patients with wild-type KRAS genes. The cetuximab therapy group revealed that patients with wild-type KRAS tumors had a response rate to cetuximab that was 12.8 percent, compared to a 1.2 percent response rate in patients with a mutated KRAS gene.6

Mutations of the KRAS gene occur as point mutations in codons 12 and 13 of exon 2. These mutations occur early in the development of mCRC carcinogenesis. Thirty-five to 40 percent of colorectal cancer (CRC) cases have KRAS mutations. KRAS mutation incidence is identical among all stages of CRC. Identification of KRAS mutations are considered to be a predictor of testing resistance to anti-EGFR monoclonal antibody therapy.3 The American Society of Clinical Oncology Provisional Clinical Option has issued a recommendation that all patients with mCRC that are candidates for anti-EGFR monoclonal antibody therapy must have tumor cells tested for the presence of KRAS mutations prior to initiating drug therapy.7 If the results show a KRAS mutation in codons 12 or 13, patients should not receive anti-EGFR monoclonal antibody therapy due to predicted resistance.

**Testing for KRAS Mutations**

KRAS mutations are detected by the DxS-K-ras test kit. It can detect seven somatic mutations on codons 12 and 13 on the KRAS gene. The kit has seven primers that are specific in detecting the most common mutations in codons 12 and 13. These primers are complementary to the KRAS gene immediately adjacent to the mutation sites. Each primer has a unique sequence at the 3' end specific for the mutation. During polymerase chain reaction (PCR) amplification, the primers attach to the template strand and only the primer with the complementary nucleotide at the 3' end will extend the mutated target DNA.5 Taq DNA polymerase is used in this test because it is very effective in distinguishing the differences between a match and mismatch nucleotide at the 3' end of a PCR primer. If the primer completely matches, amplification will occur with full efficiency; in the case of a 3' nucleotide base pair mismatch, amplification is reduced. This means only the mutated strand that matches the primer will be able to be extended. Amplification is detected using Scorpions, which are bifunctional molecules with a PCR primer covalently linked to a fluorescent probe. The fluorophore in the probe reacts with a quencher in the probe which results in a reduction in fluorescence. During the PCR amplification the probe binds to an amplicon, causing the fluorophore and quencher in the probe to become separated and increasing the amount of fluorescence observed in the reaction tube. Mutated KRAS genes will demonstrate a greater fluorescence reaction than wild-type KRAS genes because the mutated genes have a greater amount of amplification during PCR than the wild-type KRAS gene.8
Alternative Treatment Options for Patients with KRAS Mutations

The KRAS oncogene is the most commonly mutated gene in different human cancers and, due to its constitutive activity, it has the ability to bypass EGFR signaling cascade, therefore conferring resistance to anti-EGFR therapies such as cetuximab. Since patients with mCRC harboring KRAS mutations do not show a clinical response to cetuximab, they will have to consider other treatment options in order to control and treat their cancer. Some of these options include therapy that targets molecules downstream of RAS proteins such as RAF inhibitors. RAF is an effector molecule downstream of RAS in the ERK signaling pathway, making it a potential target for treating KRAS mutated tumors. Sorafenib, one of the first RAF inhibitors, has multikinase inhibitory actions against CRAF, BRAF, V600E mutant form of BRAF, vascular endothelial growth factor receptor (VEGFR) and platelet derived growth-factor receptor (PDGFR). Sorafenib has been approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma; however it is a relatively weak RAF inhibitor. Another option is using a combination of targeted agents. Since RAS activation results in activation of various branching pathways, blocking one downstream target of RAS will theoretically not be enough to inhibit tumor growth. Dual-targeted or multi-targeted therapy may be more efficient in eliminating cancer cells and fighting drug resistance in those patients with KRAS mutations.3

Trastuzumab

Trastuzumab (Herceptin®) is a human epidermal growth factor receptor 2 (HER2) antagonist. It is indicated as a treatment option in HER2 overexpressing cancers such as breast cancer in combination with doxorubicin, cyclophosphamide and paclitaxel or docetaxel; metastatic breast cancer as an adjuvant treatment with paclitaxel or used alone; and metastatic gastric or gastroesophageal junction adenocarcinoma in conjunction with cisplatin, capecitabine or 5-FU.9

Epidermal growth factor receptors (HER) dimerize upon ligand binding, thereby activating the receptor’s tyrosine kinase activity. There are four types of HER proteins: HER1, HER2, HER3 and HER4. HER2 has no endogenous epidermal growth factor ligand, but has been determined to be the most preferential binding partner for dimerization with HER1, HER3 and HER4 and therefore acts primarily as a co-receptor.10 These heterodimeric receptors have altered phosphorylation sites and cause modified activity. The HER2 heterodimers decrease the internalization of the receptor thereby amplifying and diversifying the altered signaling pathways. These signals ultimately lead to the formation of cancer through increased cellular proliferation and, potentially, metastasis of these cancers by increasing the cellular migration. It has been observed that HER2 is immunogenic, as many cancer patients express cytotoxic T-lymphocytes (CTL) which target HER2.11 Trastuzumab inhibits this cellular proliferation and migration by binding to HER2 and inducing antibody dependent cellular cytotoxicity (ADCC). It also causes an upregulation of the MHC-class 1 receptors containing the HER2 epitope in overexpressing cancer cells.11
testing prior to prescribing trastuzumab.

**Motivations and Limitations to Pharmacogenomic Drug Development**

Although pharmacogenetic testing has not become commonplace in all pharmaceutical settings, it is becoming increasingly prevalent before prescribing and to determine dosing for many oncology treatments. Many different types of cancer can now be identified based upon the specific genetic factors present. Cancer treatments are now being tailored to target these specific mutations, allowing these treatments to be more specific and efficacious. All chemotherapeutics have the potential for life-threatening adverse effects and should therefore not be prescribed unless the potential benefits outweigh the risks, a determination which cannot be conclusively made for some drugs without the use of genetic testing.

The limitation to this testing and development of genetically targeted drugs lies within the fact that the current costs to develop these medications do not cover the potential financial gains from these developments. Although the financial gains may not meet the costs of development, the quality of life (QOL) improvements gained by patients from these medications justify continued research. A 2008 study in Sweden demonstrated that the costs of FISH testing and concurrent treatment with trastuzumab for positive results (cost approximately $63,000) provided a gain of almost 1.5 quality adjusted life years (QALY). The average costs of these treatments were below the typical willingness to pay threshold and therefore this treatment regimen is superior to chemotherapy without FISH testing, which provided a lower QALY improvement. Another limitation to the implementation of more frequent genetic testing is the lack of pharmaceutical studies currently conducted on the effects of genetic variation on drug metabolism and overall effect. This kind of research would allow for the research and development of more targeted medications and could also potentially decrease the frequency of adverse events and toxicity by ensuring chemotherapeutics or other drug agents are only used within populations which will see benefits outweighing the risks associated with the drug treatment course.

**Conclusion**

The benefits of pharmacogenomics have already been observed in chemotherapy through the cases of cetuximab and trastuzumab. Both agents have demonstrated effectiveness in oncology patients possessing specific genetic biomarker characteristics. Cetuximab has been shown to improve outcomes in metastatic colorectal cancers as well as head and neck squamous cell carcinomas positive for EGFR. Trastuzumab has shown benefit in HER2 overexpressing cancers affecting the breast tissue and gastrointestinal tract. Utilizing genetic testing is essential for appropriate use of these drugs. Personalized treatments can greatly improve chances of survival through earlier administration of effective drug therapy and decreased exposure to toxic antineoplastic agents unlikely to provide benefit to the patient. Developing clinical pharmacy services in pharmacogenomics is one possible step in implementing the routine use of personalized drug therapy. Pharmacy services could include providing guidelines to physicians regarding genetic testing, initial drug selection and dosage adjustments. Although pharmacogenomics is still in the early stages in practice, pharmacists can play a vital role in the implementation and use of pharmacogenomics in therapeutic decision making.

**References**