The Importance of Genetic Diversity Considerations For Cancer Drug Development

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Differences in ethnicity, also referred to as genetic diversity, are becoming increasingly recognized as important factors of variations in drug responsiveness. In the field of anticancer medications, the same doses are often prescribed to people of different ethnicity without consideration of potential differences in metabolism as it relates to genetic variation. Recently we were able to speak to Dr. Aaron Williams. Dr. Williams, holds a Pharm.D., M.D. and an M.B.A. He is a radiation oncologist in private practice. He is also CEO of Oncology, Inc., a company that develops and manages cancer treatment centers. Dr. Williams has published several peer reviewed articles related to cancer and has presented at several national and international conferences. Dr. Williams agrees that diversity can result in differences in the recommended safe or effective dose of a drug in different populations, as well as ineffective therapy. He explains “Genetic differences explain a fraction of the larger differences observed regarding chemotherapeutic toxicity and response seen in cancer treatments. Other factors include environmental contributors such as smoking and alcohol use, which have a huge influences on metabolism and can be ethnically divergent.” Dr. Williams continued, “Ethnic differences for anticancer agents have only recently begun to be realized, given the narrow therapeutic index of most chemotherapeutics.” Dr. Williams explains that identifying genetic variants that contribute to the sensitivity that is seen in chemotherapeutic drugs has the potential to favorably impact cancer care through personalized medicine. “Recognizing pharmacoethnicity allows for more studies that are focused on genetic variants that are specific to a population of cancer patients. These genetic variants can lessen the effectiveness of specific anticancer drugs, within a specific group or ethnicity. Understanding these genetic factors has the potential to inform drug developers, as well as clinicians, and patients about which drugs are more effective in specific demographics. In other words, it could increase the efficacy regarding the effectiveness of anticancer drugs and take the guess work out of treating patients with cancer. We could identify genetic differences in cancer treatments.” Additionally, it has been pointed out that, ideally, we must consider each individual's genetic make-up in the context of environmental and regional differences that may also be important within a population (1).

Drugs such as 5-fluorouracil (5-FU) are members of the antimetabolites family, which includes various chemotherapeutics. 5-FU is commonly used to treat anal, breast, colorectal, esophageal, stomach, pancreatic, and skin cancers. It has been shown that the toxic effects seen in African-Americans who use this drug may be due to them having a significantly lower number of peripheral blood mononuclear cell levels of dihydropyrimidine dehydrogenase (DPD) activity, which is the rate-limiting enzyme of 5-FU catabolism (2). Another study of breast cancer patients showed several variations of enzymes (CYP3A4, CYP3A5, and CYP2B6) found in African-Americans, which are required to activate and metabolize a family of anticancer drugs known as Alkylating Agents, specifically cyclophosphamides. The hypothesis can be drawn that certain variations or polymorphisms that prevent the activation of cyclophosphamide could result in ethnic-specific drug exposure differences (3). If a person whose ethnicity, or genetic variation does not favor the activation and metabolism of an anticancer drug, the

possibility of a successful treatment is very low. The same can be said for anthracyclines, specifically doxorubicin, which has been shown to be cardio toxic to African-Americans (4-6), while Vinca Alkaloids (Vincristine) have been shown to cause permanent neuropathy in Caucasians(7).

Acknowledgement of the differences in drug metabolism based on ethnicity in cancer therapeutics is important in worldwide drug discovery and development. We should embrace our genetic differences and promote the development of unique studies that include genetically diverse populations who have specific clinical phenotypes. Addressing genetic diversity could improve drug efficacy for all, making individual treatment based on a person's unique genetic make-up.

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