The Relationship of Genetics, Nursing Practice, and Informatics Tools in 6-Mercaptopurine Dosing in Pediatric Oncology

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Abstract

An antileukemic agent prescribed for pediatric oncology patients during the maintenance phase of therapy for acute lymphoblastic leukemia, 6-mercaptopurine (6-MP), is highly influenced by genetic variations in the thiopurine S-methyltransferase enzyme. As such, 6-MP must be dosed so that patients with 1 or 2 inactive thiopurine S-methyltransferase alleles will not incur an increased risk for myelosuppression or other toxicities. Informatics tools such as clinical decision support systems are useful for the application of this and similar pharmacogenetics information to the realm of nursing and clinical practice for safe and effective patient care. This article will discuss pharmacogenetics and the associated use of 6-MP; present implications for nursing practice; identify informatics tools such as clinical decision support systems, which can greatly enhance the care of patients whose treatment is based on critical genetic information; and examine the relationship of genetics, nursing practice, and informatics for 6-MP dosing in pediatric oncology.

Keywords

pharmacogenetics, dosing, 6-mercaptopurine, nursing practice, informatics, clinical decision support

The typical pediatric oncology patient will have many medications prescribed over the course of his or her treatment. Due to the vulnerable nature and health fragility of this population, it is of utmost importance that medications are prescribed for optimum efficacy, function in the desired way, and produce the desired effect without causing adverse side effects or toxicities. Pharmacogenetics, the study of a patient's genetic information to identify gene variants and their subsequent influence on drug response (Prows, 2011), involves using certain drugs in accordance with individual patients' genetic variations and anticipated responses. For the pediatric oncology population, 6-mercaptopurine (6-MP) is one such drug that demands specialized knowledge of patients' genotypes for safe and appropriate use (Relling et al., 2011).

This article will discuss pharmacogenetics and the associated use of 6-MP; present implications for nursing practice; identify informatics tools such as clinical decision support systems (CDSSs), which can greatly enhance the care of patients whose treatment is based on critical genetic information; and examine the relationship of genetics, nursing practice, and informatics for 6-MP dosing in pediatric oncology.

Pharmacogenetics

Due to the impact of genetics on drug therapy, providers face difficulty in prescribing drugs—even those commonly used—for similar effect among patients (Bartlett, 2011). Genetics is believed to play a large part in individual drug response and may affect between 20% and 95% of variability in the processes of pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) (Bartlett, 2011). One goal of pharmacogenetics is the prediction of which drugs may help or harm a patient according to his or her specific genetic profile. A secondary goal, and more relevant to this discussion, is the identification of appropriate medication dosages so that inefficacy, drug reactions, and serious or adverse effects may be avoided (Bartlett, 2011; Prows, 2011).

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6-MP Usage and Dosing

6-Mercaptopurine is an antileukemic drug used in combination with methotrexate (MTX) during the maintenance phase of therapy for acute lymphoblastic leukemia (ALL), the most common childhood cancer (de Beaumais et al., 2011; Schmiegelow, Nielsen, Frandsen, & Nersting, 2014). The benefit of combination 6-MP/MTX maintenance therapy has been demonstrated by improvements in long-term remission rates for children with ALL (Gehan & Freireich, 2011; Schmiegelow et al., 2014). Moreover, significantly higher relapse rates have been associated with inadequate physician compliance or patient adherence to the oral 6-MP regimen (Schmiegelow et al., 2014). As much as a 2.7-fold increase in risk of relapse has been correlated with poor patient adherence, signifying the importance of the role of 6-MP in disease remission (Bhatia et al., 2015).

The metabolism of 6-MP is highly affected by genetic polymorphisms of the thiopurine S-methyltransferase (TPMT) enzyme. At conventional 6-MP doses, individuals who have 2 inactive TPMT alleles experience significantly greater 6-MP antileukemic activity and are consequently at 100% risk of experiencing life-threatening myelosuppression. Those with 1 inactive allele have a 30% to 60% risk of myelosuppression due to moderately heightened 6-MP activity, while those with 2 active alleles are at significantly lower risk due to normal 6-MP activity (de Beaumais et al., 2011; Relling et al., 2011). Approximately 0.3% of Caucasians and African Americans are deficient in both alleles, and approximately 5% to 13% are deficient in 1 allele (Brownstein et al., 2012; Schmiegelow et al., 2014). Starting doses for patients with 1 inactive allele should be lower than standard (30% to 70% of full dose). For patients with 2 inactive alleles, dosing should be significantly reduced in amount (at least 10-fold or 90%) and frequency (Relling et al., 2011). Therefore, in order to appropriately dose 6-MP, TPMT genotyping should be conducted before initiation of treatment with 6-MP in order to identify those patients at high or moderate risk for myelosuppression and other toxicities such as infection and hepatotoxicity (Brownstein et al., 2012; de Beaumais et al., 2011).

Nursing Practice Implications

The arrival of personalized medicine has triggered a rise in the use of genomics within health care (Greco & Mahon, 2012). As increasing numbers of patients are being treated with targeted and personalized therapies based on genetic profiles, nurses must understand the implications of genetics on nursing practice. Essential objectives include (*a*) comprehension of the link between genetics and patients' drug responses, (*b*) identification of the corresponding changes required in clinical practice, and (*c*) preparation to fully educate patients and families about the manner in which pharmacogenetics affects their care.

Nursing Practice and 6-MP

The first objective, maintaining a personal nursing knowledge of genetics and its effects on drug response and health, is vital to the provision of optimal patient care. In 2006, the Consensus Panel on Genetic/Genomic Nursing Competencies published a recommendation that "all nurses should understand the relationship of genetics to treatment selection and monitoring of treatment effectiveness, and should be able to identify patients who may benefit from genetic or genomic assessment" (Bartlett, 2011, p. 27). Nurses have been found to increase personal knowledge of genetics through independent and collaborative learning activities and, as a result, effectively apply the information to clinical practice (Junglen, Pestka, Clawson, & Fisher, 2008). In addition to this second objective of knowledge application, nurses are expected to provide accurate and understandable information to patients and their families (Greco & Mahon, 2012), thus addressing the final objective. Within the context of pharmacogenetics and 6-MP, nursing actions should involve comprehending, safely practicing, and providing suitable education with respect to genetics and the influence of patients' genotype on 6-MP metabolism and subsequent dosing requirements. Education should occur at the time of pharmacogenetic testing, when results are given to the patient and family, and should be reinforced periodically throughout treatment (Haga & Mills, 2015). Patients and families should also be instructed how to monitor for and report any signs of adverse drug reactions, myelosuppression, or toxicity (eg, bleeding, lethargy, fever, pallor, pain) (Prows, 2011). Given the technical nature of genetics and the quickly increasing volume of information, education must be given on a scale that is easily understood by patients and families (Greco & Mahon, 2012).

Advance practice registered nurses (APRNs) are also uniquely positioned to support and utilize genetic knowledge for optimal patient care. These nurse leaders may work as researchers, staff educators, administrators, or as providers who are responsible for the direct clinical care of patients (McGonigle & Mastrian, 2012). As health care grows into the genomic era, APRNs should prepare to step into leadership roles within health care organizations in order to assist with the transition of genetic knowledge to clinical practice (Greco & Mahon, 2012).

Nursing Practice Barriers

There do exist, however, educational and organizational barriers to the integration of pharmacogenetics knowledge

into nursing practice. A lack of understanding of the need for knowledge, inadequate clinical awareness about potential adverse events, and inconsistent application of knowledge can be eliminated by increasing the availability and scope of pharmacogenetics education (Crews, Hicks, Pui, Relling, & Evans, 2012; Dunnenberger et al., 2015; Hopkins et al., 2006). Nurse leaders can support increased education and interprofessional collaborative learning as well as strive to mitigate organizational barriers such as the absence of or lack of access to clinical guidelines (Haga & Mills, 2015; Hopkins et al., 2006). To minimize these difficulties in the area of pharmacogenetics, some institutions have implemented informatics tools known as clinical decision support systems (CDSSs). Nurses have been involved in the development of these tools for several years, addressing such areas as care planning, triage, and the evaluation of clinical decisions (Anderson & Willson, 2008). The development of tools to inform and guide health care professionals' clinical decisions with respect to pharmacogenetics helps bridge the gap between research evidence and practice implementation (Anderson & Willson, 2008).

Informatics Tools

Defined as technological devices used for managing and communicating information, informatics tools vary in scope and purpose (McGonigle & Mastrian, 2012). Types used for managing and communicating pharmacogenetic information include electronic medical records (EMRs) that house genetic information, dosing algorithms based on genetic information, and computerized provider order entry (CPOE) systems. EMRs can be useful for clinical decision making by providing guidance about ordering genetic tests, documentation and interpretation of results, application of information for treatment and screening, and referral to genetic counseling (Hudson, 2011). Dosing algorithms can be integrated into an EMR in order to support prescribing practice (Bartlett, 2011), and CPOE systems can utilize genetics information after buildup of the pharmacogenetics knowledge base (Welch & Kawamoto, 2013).

However, another type of health informatics tool that has come to the forefront of clinical information management is the CDSS. These systems are designed to provide knowledge and patient information in order to assist providers with real-time clinical decisions (McGonigle & Mastrian, 2012). They intelligently filter or present information and recommendations that are standardized, evidenced-based, and ultimately actionable for providers in daily practice (Kawamoto, Houlihan, Balas, & Lobach, 2005; Osheroff et al., 2007; Welch & Kawamoto, 2013). The vast breadth of the genetics knowledge base lends itself to integration with CDSSs; linking pharmacogenetics information with these systems can assist in the transition

of genetic knowledge into clinical practice. CDSSs should therefore be routinely provided in the clinical setting for the most effective utilization of pharmacogenetic information and the enhancement of patient care (Welch & Kawamoto, 2013).

6-MP Management

In 2011, the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institute of Health's Pharmacogenomics Research Network published guidelines for drug dosing based on TPMT genetic status (Relling et al., 2011; Relling & Klein, 2011). These guidelines are meant to "translate laboratory test results into actionable prescribing decisions for specific drugs" (Relling & Klein, 2011, p. 464). Ideally, such results of TPMT genetic testing would be linked through CDSS tools so that providers desiring to prescribe, dispense, or administer 6-MP would have the applicable test results and CPIC guidelines readily available (Relling & Klein, 2011).

One of the first instances of a CDSS used for 6-MP management for the pediatric oncology population was a platform created by Boston Children's Hospital's Clinical Pharmacogenomics Service (CPS). Noting the challenges of identification of gene variants, knowledge of genotype before prescribing, and integration of genetic information with EMRs, CPS proposed a solution: it standardized TPMT genotype testing hospital-wide. This was a proactive action, for despite the presence of Food and Drug Administration warning labels for TPMT testing with 6-MP and the presence of the aforementioned CPIC dosing guidelines, testing was not universal due to difficulty assimilating the CPIC guidelines with CDS and EMR systems. Consequently, Boston Children's CPS created its own pharmacogenomics platform with models and specifications to support CDSS rules based on a patient's genotype, and streamlined TPMT testing so that ordering, testing in-house, and providing results to the clinician became routine practice. A single clinical workflow was established: a Clinical Laboratory Improvement Amendments–certified laboratory uses the CDSS rules to run, analyze, and interpret the TPMT genetic testing; results are generated automatically based on genotype information and reviewed manually; and reports are then uploaded into the EMR along with specialty flow sheets that enable viewing of allele status and the resulting interpretation. Providers are then able to appropriately dose 6-MP according to the reports' specifications. This platform appears to be successful, as Boston Children's Hospital intends to expand it to include additional gene-drug pairs (Brownstein et al., 2012).

Similarly, other institutions in the United States have recently developed and implemented CDSSs for the purpose

of preemptive pharmacogenetic testing for pediatric prescription of 6-MP and other medications. The system at St. Jude Children's Research Hospital stems from a clinical research protocol opened in May 2011, PG4KDS, in which common pharmacogenetics tests were incorporated into routine care, thus allowing results to be made available preemptively. The current system utilizes genotyping results that have clear gene-drug recommendations such as the CPIC guidelines as well as their clinically relevant interpretations. This information and the corresponding clinical priority status (eg, high risk, actionable) are typically placed into the EMR before relevant drugs are prescribed. In addition, interruptive pre- and posttest CDSS alerts notify providers if specific drugs such as 6-MP are prescribed before genotype testing is completed or when affected drugs are prescribed for those with high-risk genotypes, respectively (Bell et al., 2014; Dunnenberger et al., 2015; Evans, Crews, & Pui, 2013). Vanderbilt University Medical Center's system grew from the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) project, which was started in September 2010 for adult cardiac medications. It has since been further developed to include preemptive pharmacogenetic testing for drugs commonly prescribed for pediatric patients, including 6-MP in 2013. Patient pharmacogenetic information is integrated with the EMR once gene-drug interactions are deemed actionable, and clinical decision support is presented to providers when they prescribe drugs for patients with affected genotypes (Dunnenberger et al., 2015; Peterson et al., 2013; Pulley et al., 2012). Both institutions have experienced notable progress and success with their CDSSs thus far, reporting high percentages of patients with actionable test results (78% and 91%, respectively) (Dunnenberger et al., 2015) and St. Jude reporting appropriate prescription guidance for 95% of affected patients (Bell et al., 2014).

Genetics, Nursing Practice, and Informatics in 6-MP Dosing

There is indeed potential for the field of informatics to assist nursing practice by providing patient genetic information for appropriate 6-MP management. The full benefit for the pediatric oncology population will be realized as the study of pharmacogenetics and its incorporation into clinical practice develops. However, we have seen successful demonstrated examples of the relationship of these components: the development and use of CDSSs at Boston Children's Hospital, St. Jude Children's Research Hospital, and Vanderbilt University Medical Center. These institutions recognized that a population-wide 6-MP dosing requirement based on patient genotype should be addressed, and therefore formulated CDSSs to support the use of that genotype information in practice. Informatics tools such as EMRs with or without dosing

algorithms and CPOE may certainly be used for the management and communication of 6-MP knowledge. However, other institutions would ideally follow these organizations' lead and implement CDSSs that follow the CPIC guidelines for 6-MP dosing for greatest effectiveness and enhanced patient safety. The nursing profession can likewise assimilate into practice the use of both pharmacogenetics knowledge and informatics tools for 6-MP. Nurses must be knowledgeable about the basics of genetics and pharmacogenetics and translate that knowledge into appropriate patient education, ensuring that patients and families understand how genetic information is incorporated into the 6-MP dosing scheme and how to monitor for symptoms of toxicities. APRNs must be prepared to integrate knowledge of pharmacogenetics and 6-MP into their clinical practice, develop staff educational opportunities, or support organizational efforts to remove barriers to the integration of pharmacogenetics into practice.

In summary, drugs would ideally produce only the desired therapeutic action with minimal occurrence of adverse effects, and proper dosages could be calculated easily and precisely (Bartlett, 2011). Much time and research will be required to make this situation a reality and clinically useful pharmacogenetics testing routine. This need to translate pharmacogenetics information into clinical practice is a gap CDSSs can fill (Bartlett, 2011; Welch & Kawamoto, 2013). Implementation of these systems indicates marked progress toward the full realization of the potential of genetic personalized medicine, and as the science of pharmacogenetics advances, nursing practice will likewise be empowered via the application and use of relevant clinical decision support systems and informatics tools.

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