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A review of the literature on the relationships between genetic polymorphisms and chemotherapy-induced nausea and vomiting

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ABSTRACT

Despite current advances in antiemetic treatments, between 30% to and 60% of oncology patients experience chemotherapy-induced nausea (CIN) and 13% to 33% report chemotherapy-induced vomiting (CIV). Inter-individual differences are observed in the occurrence and severity of chemotherapy-induced nausea and vomiting (CINV). This review summarizes and critiques studies on associations between occurrence and severity of CINV and polymorphisms in serotonin receptor, drug metabolism, and drug transport pathway genes. Sixteen studies evaluated the associations between the occurrence and/or severity of CINV and single nucleotide polymorphisms (SNPs). Across these studies, three SNPs in 5-hydroxytryptamine receptor (*5-HT3R*) genes, two alleles of the cytochrome P450 family 2 subfamily D member 6 (*CYP2D6*) gene, and three SNPs in ATP binding cassette subfamily B member 1 (*ABCB1*) gene were associated with the occurrence and severity of CINV. Given the limited number of polymorphisms evaluated, additional research is warranted to identify new mechanisms to develop more targeted therapies.

1. Introduction

Despite current advances in antiemetic treatments, between 30% to 60% of oncology patients experience chemotherapy-induced nausea (CIN) and 13.3% to 32.5% report chemotherapy-induced vomiting (CIV) (National Comprehensive Cancer Network (NCCN), 2017; Cohen et al., 2007; Bloechl-Daum et al., 2006). Despite the use of guideline directed antiemetic regimens, CIN continues to be one of the most severe side effects of chemotherapy (CTX) (Hofman et al., 2004). Inter-individual differences are observed in the occurrence and severity of chemotherapy-induced nausea and vomiting (CINV). Phenotypic characteristics associated with increased risk of CINV include: age under 50 years, female gender, higher trait anxiety, a history of motion sickness, a history of morning sickness, decreased alcohol intake, dehydration, malnutrition, recent surgery, and receipt of radiation therapy (Janelsins et al., 2013; Warr et al., 2011; Hesketh et al., 2010; Molassiotis et al., 2014).

Treatment characteristics associated with increased risk for CINV include: higher pretreatment expectations for CINV; susceptibility to conditioned responses triggered by odors and tastes in the oncology clinic; occurrence of CINV during a previous CTX treatment; and feelings of warmth, dizziness, or lightheadedness after CTX (Molassiotis et al., 2016; Roscoe et al., 2011). In addition, the intrinsic emetogenic potential of the CTX is an important factor that contributes to the occurrence and severity of CINV (Basch et al., 2011; Hesketh et al., 2016; Grunberg et al., 2005; Hesketh et al., 1997). Finally, lack of adherence with the antiemetic regimen during and following CTX increases the risk for CINV (Molassiotis et al., 2014).

While these phenotypic characteristics help to identify high risk patients, they do not explain all of the inter-individual variability in the occurrence and severity of CINV. For example, in a study of risk factors for antiemetic failure (Sekine et al., 2013), 46% of the patients with three risk factors (i.e., female gender, younger age, no history of alcohol use) and 9% of the patients with no risk factors experienced antiemetic treatment failure. Recent evidence suggests that polymorphisms in genes involved in the nausea and vomiting pathways may influence oncology patients' risk for CINV and/or their responses to antiemetics. To date, four reviews have summarized findings from studies on associations between antiemetic efficacy and genetic polymorphisms in oncology patients receiving CTX (Trammel et al., 2013; Perwitasari et al., 2011a; Sugino and Janicki, 2015; Kiernan, 2016).

In the first review (Perwitasari et al., 2011a), findings from six pharmacogenetic studies of antiemetic efficacy were summarized. The specific genes evaluated across these six studies were: 5-hydroxytryptamine 3A receptor (*HTR3A*), *HTR3B*, *HTR3C*, ATP binding cassette subfamily B member 1 (*ABCB1*), and cytochrome P450 family 2

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subfamily D member 6 (*CYP2D6*). The second review focused on an evaluation of differences in the efficacy of 5HT3 receptor antagonists associated with a number of genetic polymorphisms (Trammel et al., 2013). While focused on a single mechanism, this review extended the findings from the previous review (Perwitasari et al., 2011a) with a summary of four additional studies. The third review focused on the phamacogenetics of CINV (Sugino and Janicki, 2015). This 2015 review was organized using the major mechanisms that contribute to antiemetic efficacy. Across nine studies, seven of which were highlighted in the previous reviews (Trammel et al., 2013; Perwitasari et al., 2011a), associations between antiemetic efficacy and polymorphisms in *HTR3B*, *HT3RC*, *HT3RD*, *neurokinin-1 (NK-1) receptor*, *ABCB1*, organic cation transporter protein *(OCT1)*, and *CYP2D6* genes were described.

In the fourth narrative review that focused on the nursing implications of the pharmacogenomic studies of antiemetic efficacy (Kiernan, 2016), only one additional study was summarized. The major focus of all four papers was to summarize the pharmacogenomic findings within the context of the major mechanisms that are targeted by antiemetics to decrease CINV, namely: 5HT3, drug transport, and drug metabolism pathways.

However, none of these reviews provided a comprehensive synthesis of these studies that included a detailed description of the associations between genetic polymorphisms and the occurrence and severity of CINV; a critique of the studies' designs and the methods used to assess CINV; a description of study limitations; and directions for future research. Therefore, the purposes of this review of the relationships between genetic polymorphisms and CINV are to: 1) describe salient study characteristics; 2) summarize and critique the instruments used to assess CINV and the timing of the assessments; 3) synthesize findings on associations between the occurrence and severity of CINV and genetic polymorphisms; and 4) synthesize findings on associations between antiemetic efficacy and genetic polymorphisms.

2. Methods

2.1. Literature search

A systematic electronic literature search was conducted using three databases: PubMed®, Excerpta Medica Database (EMBASE®), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®). A combination of keywords used to identify relevant studies were: *chemotherapy-induced nausea and vomiting* or *chemotherapy-induced vomiting* or *chemotherapy-induced nausea* AND *gene* or *genetics* or *polymorphisms* or *gene expression* or *candidate genes*. Studies were included if they met the following criteria: (1) the entire sample had a cancer diagnosis; (2) oncology patients were assessed for CIN and/or CIV; (3) oncology patients were genotyped; and (4) associations between the occurrence and/or severity of CIN and/or CIV, with or without antiemetic drugs, and patient genotype were described. An additional inclusion criterion was that the studies were published in English between 2000 and 2016 because the human genome was sequenced in 2000. Studies were excluded: (1) if the timing of the CIN or CIV assessments was not reported; (2) if they evaluated postoperative nausea and vomiting or radiotherapy-induced nausea and vomiting; and (3) if genotype associations were evaluated only in the context of the pharmacokinetics of the CTX.

As shown in Fig. 1, the search strategy yielded 202 studies in PubMed®, 476 studies in EMBASE®, and 12 studies in CINAHL®. A total of 623 studies were excluded because the majority of them did not evaluate CINV. Of the 51 studies that did evaluate CINV, 35 were excluded because: 11 did not report the timing of the CIN or CIV assessment; 4 evaluated postoperative nausea and vomiting or radiotherapy-induced nausea and vomiting; 5 did not have genotype data; 1 evaluated genetic associations in the context of CTX pharmacokinetics; and 14 were review articles.

These review articles had the following foci: one was on associations between postoperative nausea and vomiting and genetic polymorphisms; five focused on the protein structure of receptors involved in CINV; four described the pathophysiology of CINV and pharmacological interventions; and the four summarized above (Trammel et al., 2013; Perwitasari et al., 2011a; Sugino and Janicki, 2015; Kiernan, 2016), described associations between antiemetic efficacy and genetic polymorphisms. Duplicate articles across the databases were removed and screened based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria (Moher et al., 2009). Based on our pre-specified inclusion criteria, sixteen studies are included in this review (Kaiser, 2002; Tremblay et al., 2003; Kaiser et al., 2004; Babaoglu et al., 2005; Fasching et al., 2008; Ward et al., 2008; Hammer et al., 2010; Perwitasari et al., 2011b; Tzvetkov et al., 2012; Fernandez-Rozadilla et al., 2013; Tsuji et al., 2013; He et al., 2014; Lamba et al., 2014; Lee et al., 2014; Pud et al., 2014; Zoto et al., 2015).

2.2. Data synthesis

These sixteen studies were summarized using the following pre-specified evaluation criteria: author, year, purpose, and study design; emetogenicity of the CTX regimen; major study outcome(s); gene(s) and associated polymorphism(s) classified by function; sample characteristics (i.e., sample size, age, gender, diagnosis, treatment setting, antiemetic treatment); assessment of CINV (i.e., instrument(s), timing of CINV assessments); genotyping methods; statistical analyses; major findings; strengths; and limitations (Supplementary Table S1). Given the heterogeneity of the descriptive data among the studies in terms of sample characteristics, assessment of CINV, timing of CINV assessments, types of genotyping methods, specific polymorphisms evaluated, and the types of CTX, the results are summarized in tabular and narrative form.

3. Results

3.1. Sample and treatment characteristics

Study characteristics – All sixteen studies used a prospective cohort design. While all sixteen studies recruited patients from the outpatient setting, four included hospitalized patients (Kaiser, 2002; Tremblay et al., 2003; Kaiser et al., 2004; Perwitasari et al., 2011b). Six studies were conducted in Germany (Kaiser, 2002; Tremblay et al., 2003; Kaiser et al., 2004; Fasching et al., 2008; Hammer et al., 2010; Tzvetkov et al., 2012), two in the United States (Lamba et al., 2014; Lee et al., 2014), two in Turkey (Babaoglu et al., 2005; Zoto et al., 2015), and one each in China (He et al., 2014), Japan (Tsuji et al., 2013), Indonesia (Perwitasari et al., 2011b), Israel (Pud et al., 2014), Australia (Ward et al., 2008), and Spain (Fernandez-Rozadilla et al., 2013).

Patient characteristics – Sample sizes ranged from 64 (Tsuji et al., 2013) to 2886 (Lee et al., 2014) patients. Six had less than 200 patients (Fasching et al., 2008; Ward et al., 2008; Hammer et al., 2010; Tsuji et al., 2013; Lamba et al., 2014; Pud et al., 2014). Across twelve studies that reported patients' age (Kaiser, 2002; Tremblay et al., 2003; Kaiser et al., 2004; Babaoglu et al., 2005; Fasching et al., 2008; Perwitasari et al., 2011b; Tzvetkov et al., 2012; Fernandez-Rozadilla et al., 2013; Tsuji et al., 2013; He et al., 2014; Pud et al., 2014; Zoto et al., 2015), the weighted grand mean age was 54.8 years. Of the remaining four studies, one did not report the patients' age (Ward et al., 2008) and three reported an age range (Hammer et al., 2010), a median age (Lamba et al., 2014), or both (Lee et al., 2014). Across fourteen studies, the weighted grand mean percentage of female patients was 51.1%. Two studies did not report the patients' gender distribution (Ward et al., 2008; Tzvetkov et al., 2012). When the study with 2886 patients was removed (Lee et al., 2014), the grand mean percentage of females was 64.3%.

Across the 16 studies, various cancer diagnosis were included (e.g., breast cancer, lung cancer, non-small cell lung cancer, lymphoma,