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Roles of pharmacogenomics in non-anthracycline antineoplastic-induced cardiovascular toxicities: A systematic review and meta-analysis of genotypes effect

Siew Lian Leong [a,b,1], Nathorn Chaiyakunapruk [a,c,d,e,1], Wichittra Tassaneeyakul [f,1], Poukwan Arunmanakul [g,1], Surakit Nathisuwan [h,1], Shaun Wen Huey Lee [a,e,i,*,1]

[a] School of Pharmacy, Monash University Malaysia, Selangor, Malaysia
[b] Faculty of Pharmacy, Cyberjaya University College of Medical Sciences, Selangor, Malaysia
[c] Center of Pharmaceutical Outcomes Research (CPOR), Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
[d] School of Pharmacy, University of Wisconsin, Madison, USA
[e] Asian Centre for Evidence Synthesis in Population, Implementation and Clinical Outcomes (PICO), Health and Well-being Cluster, Global Asia in the 21st Century (GA21) Platform, Monash University Malaysia, Selangor, Malaysia
[f] Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[g] Pharmaceutical Care Department, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand
[h] Division of Clinical Pharmacy, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand
[i] School of Pharmacy, Taylor's University Lakeside Campus, Jalan Taylors, 47500 Subang Jaya, Selangor, Malaysia

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ABSTRACT

Background: Exploration on genetic roles in antineoplastic-related cardiovascular toxicity has increased with the advancement of genotyping technology. However, knowledge on the extent of genetic determinants in affecting the susceptibility to the cardiovascular toxicities of antineoplastic is limited. This study aims to identify potential single nucleotide polymorphism (SNP) in predicting non-anthracycline antineoplastic-related cardiovascular toxicity.

Methods: We systematically searched for original research in PubMed, Cochrane Central Register of Controlled Studies, CINAHL Plus, EMBASE and HuGE Navigator from database inception until January 2018. Studies on association between polymorphism and antineoplastic-induced cardiovascular toxicity in patients treated for cancer of all antineoplastic agents were included except for anthracycline. Case reports, conference abstracts, reviews and non-patient studies were excluded. Data extracted by two independent reviewers were combined with random-effects model and reported according to PRISMA and MOOSE guidelines.

Results: The 35 studies included examined a total of 219 SNPs in 80 genes, 11 antineoplastic and 5 types of cardiovascular toxicities. Meta-analyses showed that human epidermal growth factor receptor 2 (HER2) rs1136201, a risk variants (pooled OR: 2.43; 1.17–5.06, $p = 0.018$) is a potential predictors for trastuzumab-related cardiotoxicity. Gene dose effect analysis showed number of variant allele may contribute to the risk too.

Conclusions: This review found that HER2 rs1136201 can have the potential in predicting trastuzumab-related heart failure. As such, further studies are needed to confirm the validity of these results as well as determine the economic aspect of using SNPs prior to its implementation as a clinical practice.

1. Introduction

The discipline of cardio-oncology is growing rapidly with the growing of number of cancer survivors [1] and awareness of the cardiovascular (CV) toxicity as one of the most significant complications of cancer therapy [2]. Recognized CV adverse effects of cancer chemotherapies are diverse and include chemotherapy related cardiac dysfunction (CRCD), hypertension, ischemia vascular effects, coronary disease, thromboembolism and arrhythmias. Anthracyclines, alkylating agents, monoclonal antibodies included HER2-targeted agents and VEGF-targeted agents, small molecule tyrosine kinase inhibitors (TKIs), antimicrotubule, antimetabolites and proteasome inhibitors groups have been associated with CV adverse effects. Some antineoplastic causes a specific CV adverse effect, while others causes various CV

* Corresponding author at: School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, 46150 Bandar Sunway, Malaysia.
E-mail address: shaun.lee@monash.edu (S.W.H. Lee).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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adverse effects. For example, the most common CV adverse event associated with bevacizumab is hypertension [3] while trastuzumab therapy is associated with congestive heart failure and decreased left ventricular ejection fraction (DLVEF) [4]. These adverse effects can impede or disrupt cancer treatment and subsequently worsen the cancer outcomes and quality of life, increase cost of care and utilization of healthcare resources.

Risk factors for CV toxicity during cancer therapy vary among antineoplastic. History of heart failure, coronary artery disease and lower body mass index were reported to be risk factors for sunitinib-related CV adverse effects [5]. In addition, trastuzumab-induced CV toxicity is associated with prior anthracycline use, pre-existing DLVEF, hypertension, elevated body mass index and age [6]. Awareness of these risks for CV toxicity is important in early prevention, identification, and treatment of the adverse effects. Because of the incompleteness of demographic and clinical risk factors to stratify individual at risk and the growth of targeted therapeutics discovery and development, attempts to understand genetic contribution have increasingly been explored over the past few years. However, the extent of knowledge of the genetic determinants which increases susceptibility to the CV toxicities of antineoplastic is limited. Our goal was to perform a systematic review and meta-analysis of studies of antineoplastic agents to understand the contribution of genetic polymorphism to the risk of antineoplastic-induced CV adverse events.

2. Methods

2.1. Search strategy

We searched EMBASE, Cochrane Central Register of Controlled Studies, PubMed, CINAHL Plus and HuGE Navigator from inception until January 2018. Search terms used include CV toxicity and genetic. This was supplemented with a manual search of cited references from retrieved articles. Primary studies reporting the results of studies examining the association between polymorphism and antineoplastic-induced CV toxicity in patients treated for cancer were included. All antineoplastic were included except for anthracycline, which has been reported before separately [7]. Case reports, conference abstracts, reviews and non-patient or lab studies were excluded.

2.2. Data extraction

Information about geographic location, study design, participant demographics and clinical characteristics, genotyping technique and definition of cardiotoxicity were extracted by reviewers (SLL and SWHL). Effects of genotypes and number of CV adverse event for each genotype were also collected. CV adverse events were categorized as follow: decreased left ventricular ejection fraction (DLVEF), hypertension, arrhythmia, venous thromboembolism (VTE) and cardiovascular disease (CVD). We reported these data in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [8] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [9].

2.3. Quality assessment

Quality of the included studies was assessed independently by reviewers using quality of genetic association studies (Q-Genie) tool developed by Sohani et al. [10] The validation tool was developed based on the Strengthening the Reporting of Genetic Association Studies (STREGA) [11] and Strengthening the Reporting of Genetic Risk Prediction Studies (GRIPS) [12]. It consists of nine domains; rationale for study, selection and definition of outcome of interest, selection and comparability of comparison groups, technical classification of the exposure, non-technical classification of the exposure, other sources of bias, sample size and power, a priori planning of analyses, statistical methods and control for confounding, testing of assumptions and inferences for genetic analyses and appropriateness of inferences drawn from results.

2.4. Statistical analysis

We presented all data narratively. We used the odds ratio (OR) for CV adverse event, estimating 95% confidence intervals (95% CI). In studies with similar outcomes (minimum 2 studies), we performed pairwise random effects meta-analysis [13]. Heterogeneity of the studies was assessed using Cochran's Q and I^2 statistics. In the event of substantial heterogeneity, the potential causes of heterogeneity were explored with meta-regression and sensitivity analyses. Funnel plot was constructed to evaluate publication bias. Gene dose effect which compares the effect of number of allele was conducted for polymorphism with sufficient data available. All analyses were performed using Stata 15.0 (StataCorp, College Station, TX).

3. Results

3.1. Study Selection and characteristics

Our search retrieved 7883 potentially relevant articles. After screening, 187 articles were identified for review, with 152 articles excluded for various reasons: case reports ($n = 4$), conference abstracts ($n = 26$), unrelated to research question ($n = 97$), review article ($n = 14$) and laboratory studies ($n = 11$). A total of thirty-five articles describing CV adverse events of eleven antineoplastic from five drug classes were included in the current review (eFig. 1). The antineoplastic include tyrosine kinase inhibitor (axitinib, sorafenib and sunitinib), monoclonal antibody (bevacizumab, cetuximab and trastuzumab), antimetabolite (fluorouracil), alkylating agent (cisplatin and temozolamide) and immunomodulatory agent (lenalidomide and thalidomide). These studies mostly described CV events which include hypertension induced by four antineoplastic agents namely bevacizumab [14], sunitinib [15–22], axitinib [23,24] and sorafenib [25,26]; DLVEF induced by trastuzumab [27–34] and VTE induced by bevacizumab [35–37], cisplatin [38], lenalidomide [39], temozolamide [35] and thalidomide [37,40]. Majority of these studies used either the National Cancer Institute Common Toxicity Criteria version 2, 3, or 4 to assess severity of CV adverse events. The characteristics of the included studies are presented in eTable 1.

Most of the studies were cohort studies [15–30,32–36,38,39,41–48] ($n = 31$) while the remaining were case-control ($n = 3$) [31,37,40] and randomized controlled trial ($n = 1$) [14]. These studies were done in Europe ($n = 16$) [15,16,20,22,26,27,29,30,32,36,38–40,42,43,46], North America ($n = 5$) [25,28,31,33,48], Asia ($n = 5$) [21,24,34,41,44], and another 4 studies were multi-centred studies conducted in several countries. Five studies did not report the study location [14,17,35,37,47]. Thirty studies included adults in their report with eight studies did not report the age of included population. Twenty-two studies described the ethnicity of their participants [14–16,18–20,22–25,28,31,33,34,37,39–45].

The most common type of diseases examined were breast cancer ($n = 10$), renal cancer ($n = 9$), colorectal cancer ($n = 4$), multiple myeloma ($n = 3$), testicular cancer ($n = 1$), and glioma ($n = 1$). The remaining seven studies mixed type of cancer were examined. All the studies reported single type of cardiovascular adverse event except for three studies [36,38,42] which reported two cardiovascular toxicities. Twenty studies reported the genetic association with hypertension [14–26,36,42–48], eight studies each on DLVEF [27–34] and VTE [35–40,42], one study on coronary artery disease [38] and one on arrhythmia [41].

3.2. The quality of the reporting in the studies

All the thirty-two included studies were rated to be of good quality, with mean scores of >3 on all domains assessed using the Q-Genie tool (Supplementary eTable 2).

3.3. Polymorphism

The thirty-five included studies identified a total of 219 single-nucleotide polymorphisms (SNPs) in eighty genes (Table 1, eTables 3–7). Seventy-four (34%) of SNPs in forty genes were found to be significantly associated with antineoplastic-induced cardiovascular toxicities in at least one study. These SNPs were mainly associated with hypertension, decreased LVEF and VTE. However, only SNPs from vascular endothelial growth factor (VEGF) and human epidermal growth factor receptor 2 (HER2) in association with bevacizumab-related hypertension and trastuzumab-related decreased LVEF respectively have sufficient data for quantitative analysis.

Twenty studies investigated the genetic association underlying antineoplastic-related hypertension. Ten and seven studies investigated

Table 1
Summary of SNPs investigated in studies.

Hypertension		
Bevacizumab		
EGF (rs4444903)[a]	AGTR1 (rs12695902)	KLKB1 (rs4253296)
EGF (rs9992755)[a]	AGTR1 (rs12721331)	KLKB1 (rs4253315)
FIP200 (rs1129660)[a]	AGTR1 (rs1492099)	KLKB1 (rs4253327)
GRK4 (rs1419044)[a]	AGTR1 (rs2675511)	KLKB1 (rs4253331)
HT (rs1937506)[a]	AGTR1 (rs275649)	KLKB1 (rs925453)
KLKB1 (rs1912826)[a]	AGTR1 (rs2933249)	SCNN1A (rs2041375)
SV2C (rs6453204)[a]	AGTR1 (rs3772616)	SCNN1A (rs2228576)
ULK1 (rs9481)[a]	AGTR1 (rs385338)	SCNN1A (rs2286600)
VEGF (rs699947)[a]	AGTR1 (rs389566)	SCNN1A (rs3764874)
VEGF (rs833061)[a]	AGTR1 (rs4681440)	SCNN1A (rs3764875)
VEGF (rs2010963)[a]	AGTR1 (rs5182)	SCNN1A (rs3782723)
VEGF (rs3025039)[a]	ATG13 (rs13448)	SCNN1A (rs4764585)
VEGF (rs3097)[a]	ATG3 (rs9831088)	SCNN1A (rs7973914)
VEGF (rs13207351)[a]	ATG5 (rs633724)	ULK1 (rs11616018)
VEGF (rs25569394)[a]	ATG8 (rs11149841)	ULK1 (rs12303764)
VEGF (rs1005230)[a]	ATG8 (rs8060972)	UVRAG (rs1458836)
VEGF (rs35864111)[a]	BDKRB1 (rs10147171)	VEGF (rs10434)
VEGFR2 (rs1870377)[a]	BDKRB1 (rs11622768)	VEGF (rs1570360)
WNK1 (rs11064560)[a]	BDKRB1 (rs2071083)	VEGF (rs2146323)
WNK1 (rs2286028)[a]	BDKRB1 (rs2071084)	VEGF (rs25648)
WNK1 (rs2158501)[a]	BDKRB1 (rs885845)	VEGF (rs3024994)
WNK1 (rs11064519)[a]	BECN1 (rs11552192)	VEGF (rs3025030)
WNK1 (rs7953912)[a]	CYP11B2 (rs12050217)	VEGF (rs3025035)
ACE (rs4295)	CYP11B2 (rs1799998)	VEGF (rs833069)
ACE (rs4305)	CYP11B2 (rs4543)	VEGFR2 (rs2305948)
ACE (rs4309)	CYP11B2 (rs6433)	WNK1 (rs10774461)
ACE (rs4311)	FIP200 (rs17337252)	WNK1 (rs10849582)
ACE (rs4343)	GNB3 (rs5446)	WNK1 (rs10935724)
ACE (rs4357)	GRK4 (rs1010290)	WNK1 (rs11064524)
AGT (rs11568054)	GRK4 (rs1419043)	WNK1 (rs11064547)
AGT (rs2004776)	GRK4 (rs1557213)	WNK1 (rs11068756)
AGT (rs2478523)	GRK4 (rs17835422)	WNK1 (rs11611231)
AGT (rs2478543)	GRK4 (rs1801058)	WNK1 (rs12314329)
AGT (rs2478544)	GRK4 (rs2067003)	WNK1 (rs12816718)
AGT (rs2478545)	GRK4 (rs2105380)	WNK1 (rs1468326)
AGT (rs2493131)	GRK4 (rs2515936)	WNK1 (rs17223420)
AGT (rs2493132)	GRK4 (rs2857845)	WNK1 (rs2286007)
AGT (rs3789678)	KLKB1 (rs1511802)	WNK1 (rs4980968)
AGT (rs3889728)	KLKB1 (rs3087505)	WNK1 (rs4980973)
AGT (rs4762)	KLKB1 (rs3775302)	WNK1 (rs6489755)
AGT (rs5050)	KLKB1 (rs4253251)	WNK1 (rs7967755)
AGT (rs6687360)	KLKB1 (rs4253260)	WNK1 (rs953361)
AGT (rs7079)	KLKB1 (rs4253292)	WNK1 (rs2269937)
AGT (rs1926722)		
Sorafenib		
ABCG2 (rs2231137)[a]	UGT1A9 (rs72551330)[a]	ABCG2 (rs2622604)
VEGFR1 (rs9513070)[a]	ABCB1 (rs1045642)	VEGFR2 (rs2305948)
VEGFR2 (rs1870377)[a]	ABCB1 (rs2032582)	VEGFR2 (rs2305948)
UGT1A9 (rs178868320)[a]	ABCG2 (rs2231142)	CYP3A5 (rs776746)
UGT1A9 (rs6714486)[a]		
Sunitinib		
VEGF (rs833061)[a]	IL8 A > T (rs1128847)[a]	VEGFR3 (rs448012)
VEGF (rs2010963)[a]	eNOS (rs2070744)[a]	VEGFR3 (rs307821)
VEGF (rs699947)[a]	CYP3A4 (rs4646437)[a]	VEGFR3 (rs307826)
VEGF (rs1570360)[a]	ABCG2 (rs2622604)	VEGFR1 (rs9582036)
VEGFR2 (rs1870377)[a]	ABCB1 (rs1045642)	VEGF (rs3025039)
ABCB1 (rs1128503)[a]	ABCG2 (rs55930652)	CYP3A5 (rs776746)
ABCB1 (rs2032582)[a]	VEGFR1 (rs9554320)	CYP3A4 (rs2740574)
ABCG2 (rs2231142)[a]	VEGFR2 (rs2305948)	PDGFR-α (rs35597368)
Cetuximab		
FIP200 (rs1129660)		
Axitinib		
VEGRF2 (rs2305948)[a]	ABCG2 (rs2231142)	VEGFR1 (rs9513070)
Decreased left ventricular ejection fraction		
Trastuzumab		
BRINP1 (rs10117876)[a]	BRINP1 (rs7027658)[a]	CREBRF (rs201763080)
BRINP1 (rs7038923)[a]	BRINP1 (rs75912020)[a]	EYS (rs139944387)
BRINP1 (rs7041012)[a]	BRINP1 (rs76890184)[a]	FCGR2A (rs1801274)
BRINP1 (rs1160584)[a]	BRINP1 (rs58944852)[a]	FCGR3A (rs396991)
BRINP1 (rs230145)[a]	BRINP1 (rs6256837)[a]	FIG4 (rs56378532)
BRINP1 (rs230144)[a]	HER2 (rs1058808)[a]	GTF3C3 (rs146213213)
BRINP1 (rs230142)[a]	HER2 (rs1136201)[a]	KRT15 (rs78272919)
BRINP1 (rs62573809)[a]	Intergenic (rs4305714)[a]	MYADM (rs140387622)

Table 1 (*continued*)

Decreased left ventricular ejection fraction		
BRINP1 (rs16908078)[a]	LDB2 (rs55756123)[a]	PHF3 (rs139503277)
BRINP1 (rs7851490)[a]	LINC01060 (rs7698718)[a]	PLEKHA6 (rs149581993)
BRINP1 (rs7854066)[a]	RAB22A (rs707557)[a]	SFTPA2 (rs150273659)
BRINP1 (rs62573837)[a]	TRPC6 (rs77679196)[a]	ZNRF3 (rs5762940)
BRINP1 (rs76586195)[a]		
Venous thromboembolism		
Thalidomide		
PPARD (rs2267669)[a]	DCLRE1B (rs12022378)[a]	CINP (rs7011)[a]
CASP3 (rs1049216)[a]	XRCC5 (rs2440)[a]	ABCB4 (rs2302387)
SERPINE (rs2070682)[a]	IL12A (rs582537)[a]	ALDH-1A1 (rs168351)
NAT2 (rs2410558)[a]	HMMR (rs299295)[a]	ALDH-1A1 (rs610529)
TNFRSF17 (rs12922317)[a]	LEP (rs10249476)[a]	PARP1 (rs1805414)
LIG1 (rs20579)[a]	ALDH1A1 (rs2161811)[a]	VEGF (rs699947)
COMT (rs4633)[a]	ERCC6 (rs4253211)[a]	CETP (rs289747)
MT (rs13815)[a]	CHEK1 (rs506504)[a]	GAN (rs2608555)
CDKN1A (rs3829963)[a]		
Cisplatin		
PAI-1 (rs1799889)	PAI-1 (rs1799889)	Factor V (rs6025)
Factor II (rs1799963)		
Lenalidomide		
CINP (rs7011)	CDKN1A (rs3829963)	CHEK1 (rs506504)
ALDH 1A1 (rs610529)	XRCC5 (rs2440)	TNFRSF17 (rs12922317)
NFKB1 (rs3774968)		
Bevacizumab		
VEGF (rs2010963)[a]	VEGF (rs833061)[a]	FIP200 (rs1129660)
VEGF (rs13207351)[a]	ATG3 (rs9831088)	FIP200 (rs17337252)
VEGF (rs1570360)[a]	ATG5 (rs633724)	ULK1 (rs11616018)
VEGF (rs699947)[a]	ATG8 (rs8060972)	UKL1 (rs12303764)
VEGF (rs35569394)[a]	ATG8 (rs11149841)	ULK1 (rs9481)
VEGF (rs1005230)[a]	ATG13 (rs13448)	UVRAG (rs1458836)
VEGF (rs35864111)[a]	BECN1 (rs11552191)	
Temozolomide		
VEGF (rs2010963)		
Coronary heart disease		
Cisplatin		
Factor V (rs1799963)[a]	Factor II (rs6025)	PAI-1 (rs1799889)
Arrhythmia		
DYPD (rs1801159)[a]		

[a] Significant association found in at least one study; ABCB, ATP binding cassette subfamily B member; ABCG2, ATP binding cassette subfamily G member 2; ACE, angiotensin I converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin II receptor type 1; ALDH 1A1, aldehyde dehydrogenase 1 family member A1; ATG, autophagy related; BDKRB1, bradykinin receptor B1; BECN1, beclin 1; BRINP1, BMP/Retinoic acid inducible neural specific 1; CASP3, caspase 3; CDKN1A, cyclin dependent kinase inhibitor 1A; CETP, cholesteryl ester transfer protein; CHEK1, checkpoint kinase 1; CINP, cyclin dependent kinase 2 interacting protein; CREBRF, CREB3 regulatory factor; CYP11B2, cytochrome P450 family 11 subfamily B member 2; CYP3A5, cytochrome P450 family 3 subfamily A member 5; DCLRE1B, DNA cross-link repair 1B; DPYD, dihydropyrimidine dehydrogenase; EGF, epidermal growth factor; eNOS, endothelial nitric oxide synthase; ERCC6, ERCC excision repair 6, chromatin remodeling factor; EYS, eyes shut homolog (drosophila); FIG4, FIG4 phosphoinositide 5-phosphatase; FCGR2A, Fc fragment of IgG receptor IIa; FCGR3A, Fc fragment of IgG receptor IIIa; FIP200, focal adhesion kinase family interacting protein of 200 kDa; GAN, gigaxonin; GNB3, G protein subunit beta 3; GRK4, G protein-coupled receptor kinase 4; GTF3C3, general transcription factor IIIC subunit 3; HER2, human epidermal growth factor receptor 2; HMMR, hyaluronan mediated motility receptor; IL, interleukin; KLKB1, kallikrein B1; KRT15, keratin 15; LDB2, LIM domain binding 2; LEP, leptin; LIG1, DNA ligase 1; LINC01060, long intergenic non-protein coding RNA 1060; MT, mitochondrially; MYADM, myeloid associated differentiation marker; NAT2, *N*-acetyltransferase 2; NFKB1, nuclear factor kappa B subunit 1; PAI-1, plasminogen activator inhibitor-1; PARP1, poly(ADP-Ribose) polymerase 1; PHF3, PHD finger protein 3; PLEKHA6, pleckstrin homology domain containing A6; PPARD, peroxisome proliferator activated receptor delta; RAB22A, RAB22A member RAS oncogene family; SCNN1A, sodium channel epithelial 1 alpha subunit; SERPINE1, serpin family E member 1; SFTPA2, surfactant protein A2; SV2C, synaptic vesicle glycoprotein 2C; TNFRSF17, tumour necrosis factor receptor superfamily member 17; TRPC6, transient receptor potential cation channel subfamily C member 6; UGT1A9, UDP glucuronosyltransferase family member A9; ULK1, unc-51 like autophagy activating kinase 1; UVRAG, UV radiation resistance associated; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; WNK1, WNK lysine deficient protein kinase 1; XRCC5, X-ray repair cross complementing 5; ZNRF3, zinc and ring finger 3.

bevacizumab- and sunitinib-related hypertension respectively. Other antineoplastic evaluated were cetuzumab, sorafenib and axitinib. Thirty-three (21.6%) of 153 SNPs were reported to be associated with hypertension (Table 1, eTable 3) in at least one study. The vascular endothelial growth factor (VEGF) related SNPs were the most commonly evaluated genetic variants.

Six studies investigated the genetic associations underlying antineoplastic-related decreased LVEF. Trastuzumab is the only antineoplastic examined in the six studies.

Seven studies reported the relationship between SNPs and VTE induced by five antineoplastic, namely bevacizumab, cisplatin, lenalidomide, temozolamide and thalidomide (Table 1, eTable 5). Twenty-six (53.1%) of forty-nine SNPs were associated with antineoplastic-related VTE in at least one study. The SNP cyclin dependent kinase 2 interacting protein (CINP) rs7011 was the most commonly evaluated genetic variants.

3.4. SNPs in bevacizumab-related hypertension

Three retrospective cohort studies which included a total of 366 patients examining the role of five SNPs associated with vascular endothelial growth factor (VEGF) were included in quantitative analysis [43,44,47]. All the SNPs associated with increased risk of bevacizumab-related hypertension were: heterozygous and homozygous variant of VEGF −2574C > A (rs699947) [44], heterozygous and homozygous variant of VEGF −1498T > C (rs833061) [47], heterozygous and homozygous variant of VEGF −1154G > A (rs1570360) [43] and heterozygous and homozygous variant of VEGF 936C > T (rs3025039) [44]. Meta-analysis of these SNPs showed that patients with heterozygous and homozygous variant in the VEGF (rs699947, rs833061, rs1570360, rs2101963, rs3025039) were 1.56 times higher risk of developing bevacizumab-induced hypertension (Pooled odds ratio (OR): 1.56, 95% CI, 1.07–2.88, $p = 0.006$; Fig. 1). Visual inspection of funnel plots showed no clear sign of asymmetry indicating a lack of evidence of small study effect (eFigs. 2–6). Stratification of studies by the genetic variants did not show any variant which was significantly associated with an increased risk of developing bevacizumab-induced hypertension.

3.5. SNPs in trastuzumab-related decreased LVEF

Six cohort studies examined the role of human epidermal growth factor receptor 2 (HER2) variant 655A > G rs1136201 in developing cardiotoxicity [27–30,32,33] (eTable 4). In the 1322 patients examined, cardiotoxicity was defined as either a decline of 10–20% of LVEF from baseline [27–30,32]; or an absolute LVEF value of less than 45–50% [27–30,32]. The dose of trastuzumab used was a loading dose of 8 mg/kg followed by 6 mg/kg [27–30]. In the study by Beauclair et al. which included 63 HER2-positive breast cancer patients, the authors noted significant association for heterozygotes of rs1136201 with increased risk of developing cardiotoxicity [27]. Similarly, Roca et al. studied with a doubled number of HER2-positive breast cancers patients ($n = 132$) and found similar association for heterozygous and homozygous variant genotypes of rs1136201 (OR = 3.83, 95% CI: 1.11–13.18, $p = 0.025$) [29]. Pooling of studies showed that the presence of HER2 heterozygous and homozygous variant genotypes of

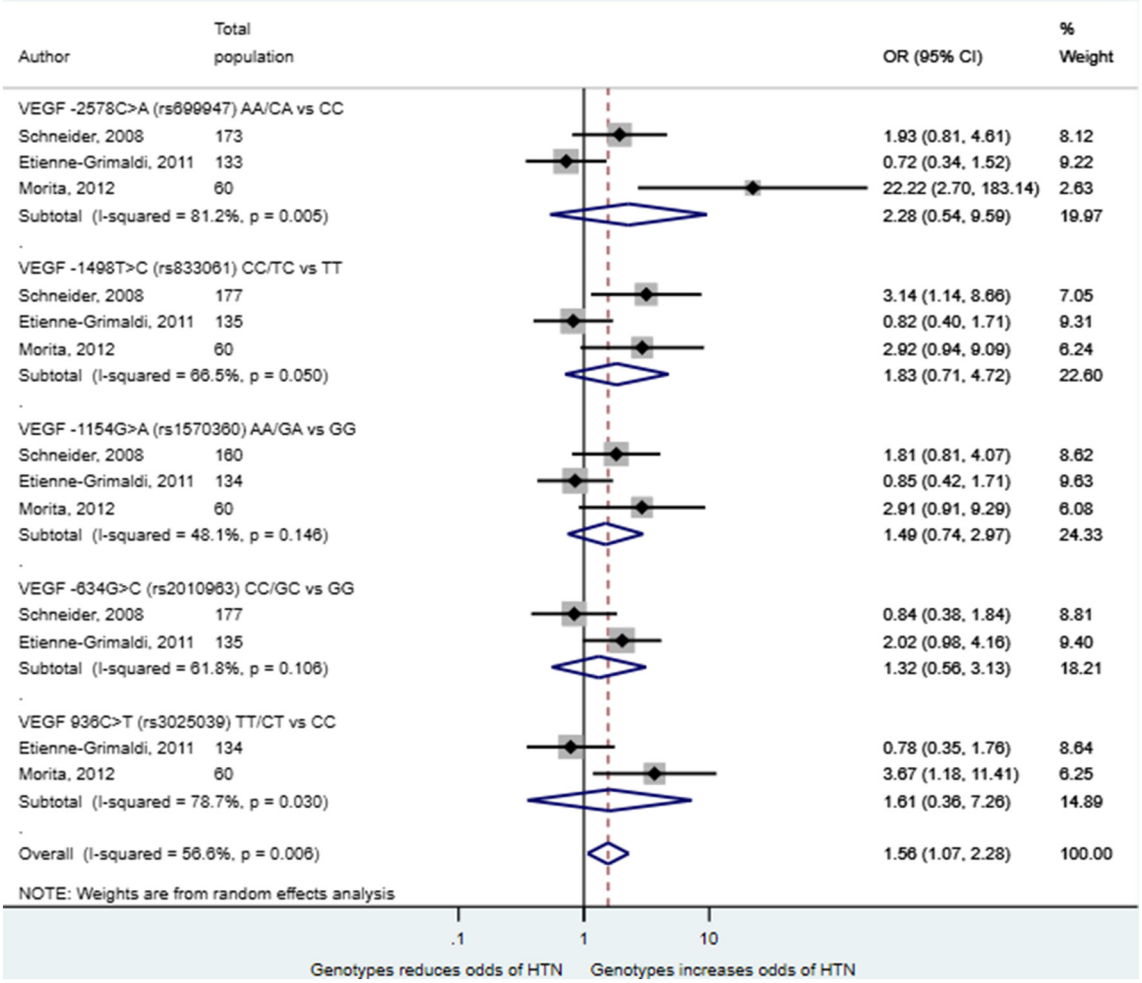

Fig. 1. Meta-analysis of genotypes associated with bevacizumab-induced hypertension (HTN). VEGF, vascular endothelial growth factor.

rs1136201 increased the risk of developing heart failure by 2.43 times (95% CI: 1.17–5.06, $p = 0.018$; Fig. 2), but not other variants. Visual inspection of funnel plots showed asymmetry for studies which had reported for the SNP rs1136201 but not other SNPs (eFigs. 7–10). By applying the trim and fill method [49], the pooled effect was changed to be a non-significant summary estimate (OR = 1.49; 95% CI: 0.80–2.78, $p = 0.205$). To further explore potential reasons for this variation, we conducted subgroup and meta-regression analysis using population and study characteristics such as region study was conducted, total sample size, genotyping method, population ethnicity as well as if the studies reported genetic variation at Hardy-Weinberg equilibrium (HWE). Subgroup analysis showed that both total sample size and genotyping method modified the odds ratio of developing heart failure (eTable 8). Meta-regression analyses also noted a similar trend that sample size and genotyping method are important factors, but they are not significant due to the small number of studies (eTable 9). For the other SNPs, there were fewer than 5 studies which had reported these associations, and thus it was not possible to use meta-regression to evaluate the relative merits of these SNPs.

Four studies examined the role of rs1058808 SNP in heart failure among patients with HER2 polymorphism [28,31–33] (eTable 4). These studies had a very similar definition of cardiotoxicity and dosage of trastuzumab in their cohort examined. In the study by Stanton et al. which included 140 HER2-positive breast cancer patients, the authors noted significant association for heterozygous and homozygous variants for reduced risk of developing cardiotoxicity [31]. Similarly, Boekhout et al. studied 206 early-stage HER2-positive breast cancer patients and found similar association for homozygous variant (OR = 0.09; 95% CI, 0.02–0.45; $p = 0.003$) [32]. However, the study by Lemieux et al. did not find significant association between heterozygous variant of rs1058808 SNP (OR = 0.19, 95% CI, 0.19–4.71, $p = 0.95$) or homozygous variant (OR = 1.62, 95% CI, 0.32–8.29, $p = 0.57$) [28]. Pooled analysis showed that the presence of rs1058808 SNP was potentially cardio-protective, and reduced the risk of developing heart failure by 31% (OR: 0.69; 95% CI: 0.47–1.02, $p = 0.061$, Fig. 2).

Table 2
Gene dose effect of trastuzumab-induced decreased LVEF.

SNPs	Pooled OR (95% CI)			p-Value[a]
	Combination (Aa/aa)	Heterozygous (Aa)	Homozygous (aa)	
HER2 655A > G (rs1136201)	**2.43**[b] **(1.17–5.06)**	1.71 (0.91–3.23)	1.24 (0.70–2.18)	0.78
HER2 1170C > G (rs1058808)	0.69 (0.47–1.02)	0.76[b] (0.48–1.19)	0.44 (0.13–1.50)	0.36
FCGR2A 131C > T (rs1801274)	1.10 (0.42–2.87)	1.06 (0.36–3.12)	1.70[b] (0.83–3.49)	0.48
FCGR3A 158 T > G (rs396991)	0.83 (0.37–1.89)	0.60[b] (0.25–1.48)	0.99 (0.41–2.41)	0.62

Bold indicate significant odds ratios.
[a] Statistical test of difference between odds ratio for Aa and aa.
[b] Greatest effect among genotypes.

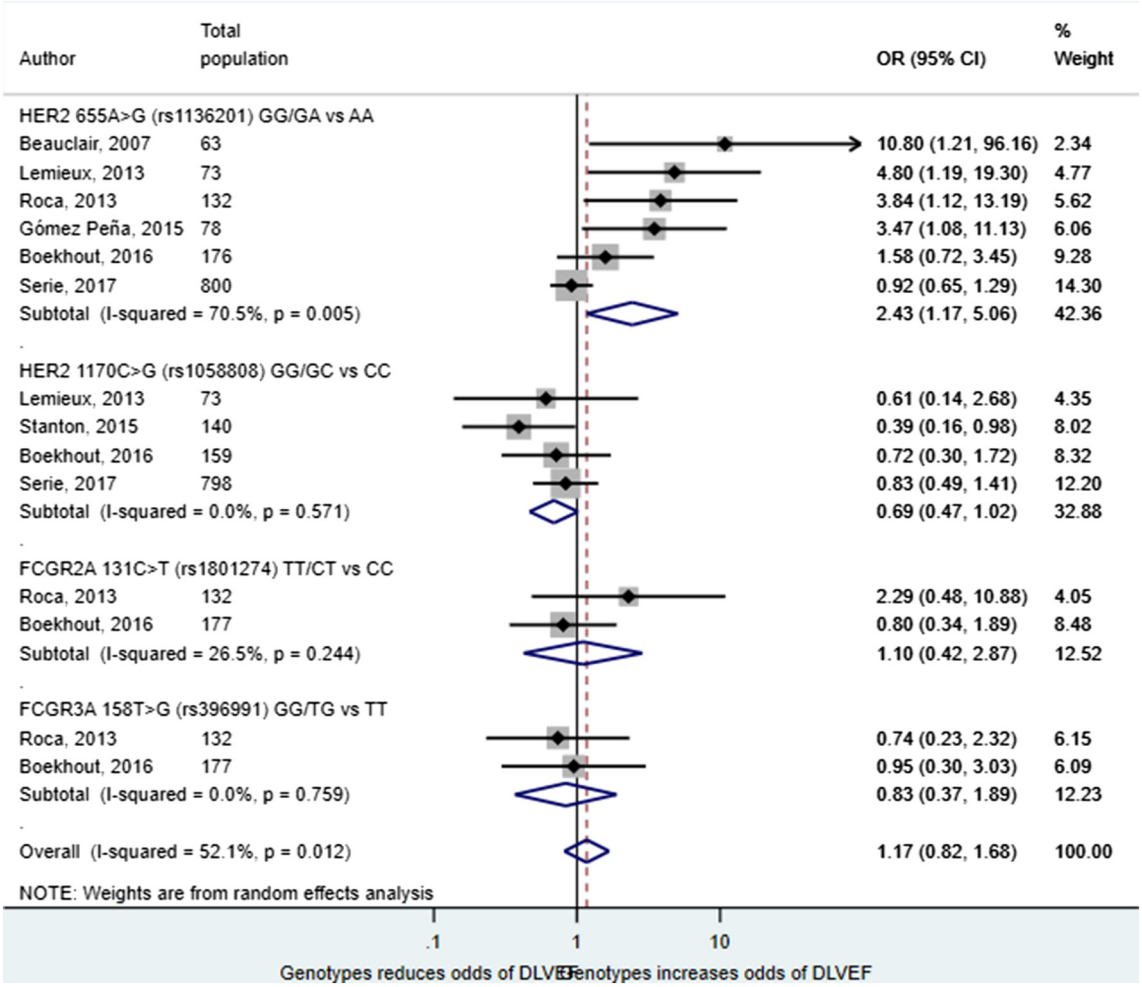

Fig. 2. Meta-analysis of genotypes associated with trastuzumab-induced decreased left ventricular ejection fraction (DLVEF). HER2, human epidermal growth factor receptor 2.

Analysis of gene dose effect showed odds ratios changed with the number of variant allele although the differences were not statistically significant (Table 2). Only FCGR2A rs1801274 has enhanced risk effect with increased number variant allele. The risk or protective effect in SNPs HER2 rs1136201, HER2 rs1058808 and FCGR3A rs396991 is stronger for heterozygous genotypes compared to homozygous genotypes. For example, heterozygous genotype of FCGR3A rs396991 has greatest protective effect (OR: 0.60; 95% CI: 0.25–1.48, $p = 0.27$) compared to homozygous (OR: 0.99; 95% CI: 0.41–2.41, $p = 0.98$).

4. Discussion

We found a total of thirty-five studies, exploring the effect of 219 SNPs on eleven antineoplastic and five types CV toxicities. All the studies utilized candidate-gene approach, and only two used genome-wide approaches [14,33]. Our findings indicate that seventy-four (34%) SNPs are significantly associated with risk of particular antineoplastic related CV toxicities. Among these findings, association of SNPs rs1136201 and rs1058808 of HER2 with trastuzumab-related cardiotoxicity was most prominent. This effect has potential clinical ramification since trastuzumab is specifically used for HER2 receptor positive breast cancer. It has been reported that the incidence of trastuzumab-induced CV toxicities are likely between 20 and 33% [50–52] which are frequently manifested as decreased LVEF (7.5%) and congestive heart failure (1.9%) [53]. While most of these side effects are often mild and reversible, the long-term implication on CV morbidity and mortality are uncertain [54]. Indeed, in patients with the SNP rs1136201 close monitoring and attention should be given to this particular cohort of breast cancer patients as they have up to 2.4 times increased risk of developing heart failure. This could include compulsory screening for the variant, which currently cost approximately USD1 per SNP.

Although the role of these SNPs in the pathophysiology of cardiotoxicity is still unknown, it has been proposed that trastuzumab-related cardiotoxicity could be related to the disruption in signaling between the HER2 receptor and ligand growth factor. It had been shown that HER2 is critical for normal myocyte growth, survival and homeostasis in mouse studies [55–57]. Studies by Crone et al. and Özcelik et al. using HER2-deficient conditional mutant mice found evidence of dilated cardiomyopathy [55,56]. Meanwhile, in-vitro study using culture of neonatal rat ventricular myocytes found that anti-HER2 related impairment of mitochondrial integrity and disruption of cellular energetics is caused by the activation the mitochondrial apoptosis pathway [57].

On the other hand, VEGF targeted therapy such as bevacizumab, sunitinib, and sorafenib have been reported to cause hypertension in patients. Bevacizumab-related hypertension is common with incidence rate for all-grade and high-grade hypertension at 25.3% and 8.2% [58] and appeared to be dose dependent [59]. High-grade hypertension especially hypertensive crisis may cause obvious cardiovascular damage and be life-threatening. As a result, optimum use and efficacy of bevacizumab is compromised. Bevacizumab has broad anti-tumour properties by inhibiting VEGFA, however, there are no validated biomarkers to predict its efficacy or toxicity. The pathophysiology of this adverse event is yet to be defined although numerous theories had been suggested including bevacizumab inhibition of VEGF decreases synthesis of nitric oxide, a potent vasodilator [60]. Thus, unsurprisingly most of the included studies examine the relationship between SNPs in VEGF and VEGFR for both bevacizumab and sunitinib. Some of these studies provide evidence on SNPs as potential biomarkers of hypertension treated with these VEGF targeted agents.

Pharmacogenetics tests paired with antineoplastic agents that are considered part of routine cancer care are increasing and appreciating the role of genetic in antineoplastic-related cardiotoxicity is the first step. Nevertheless, our study found that there were only very few studies which reported these associations and our analysis suggests that there were hints of publication bias. Pharmacogenetics testing had been recommended to individualize anthracycline therapy based on anthracycline-induced cardiotoxicity risk [61]. While SNPs could ultimately be used to mitigate risk of developing this highly morbid adverse effect, more well-designed genetic association studies with larger sample sizes are needed to confirmed and validated the results we obtained. Given the large volume of patients who receive these agents and the relative frequency of which CV toxicity occurs, it seems logical that more advanced approaches such as human genome-wide association studies or whole exome or whole genome sequencing should be undertaken with proper population stratification. Besides, preclinical molecular and novel non-human genetic research will also enhance opportunities for broader genomic analysis. Further investigation on the mechanism of SNPs rs1136201 and rs1058808 on trastuzumab-related cardiotoxicity is also recommended since it is still unknown.

Our study also observed a high level of heterogeneity in the reported meta-analyses, which limited the precision of overall estimates. For example, although meta-analysis can be performed for five SNPs in relation to bevacizumab-related HTN, the moderate to high values of I^2 values suggests that there exists heterogeneity across studies. Funnel plots for studies reporting trastuzumab-related cardiotoxicity showed the presence of publication bias. We attempted to address this using the "trim and fill" method and results became non-significant. As this method is known to perform poorly in the presence of substantial between-study heterogeneity, we attempted to address this using a meta-regression analysis. The meta-regression and subgroup analyses found that the sample size and type of genotyping method affected the odds of developing trastuzumab-related cardiotoxicity. In particular, we noted that studies with smaller sample sizes have a higher odds compared to studies that recruited >100 samples. Sanger sequencing is considered the gold standard in genotyping, but over the past few years various other methods such as PCR-RFLP and Taqman PCR have been used due to cost and turnaround time. Studies have suggested these results from the different assays are comparable. Taken together, we urge caution in interpreting the results.

This study has several strengths. Firstly, included studies examining the role of HER2 SNPs had included a relatively large sample of participants. All studies had used an objective outcome of ejection fraction and had a relatively homogenous definition of decreased LVEF. Although the participants of these studies were recruited from Europe and North America, generalization of these findings in other populations is probable with large multi-ethnic genetic studies in the future.

There are some limitations of this study which warrants discussion. Current evidence suggests that several SNPs are associated with CV toxicities. However, a number of methodological concerns may limit the interpretation and comparability of the results. Although 219 SNPs were identified, meta-analysis could only be performed for nine of the SNPs, as most of the SNPs found in this study have been studied only once. In addition, there were inconsistencies in reporting result and lacking in required data for meta-analysis, which further curbed the ability to combine the data. There was also a high level of heterogeneity in the reported analyses. While we attempted to explore the causes of such heterogeneity for all our results, the small number of studies for each SNP, which in most cases were fewer than five studies limited further analysis using meta-regression analysis. As such, findings should be interpreted with cautions due to the limited power to detect bias. The collinearity among the genotypes also did not allow for additional analysis such as network meta-analysis.

5. Conclusion

This review found that SNPs rs1136201 human epidermal growth factor receptor 2 (HER2) is a potential predictor for trastuzumab-related cardiotoxicity. These SNPs should be further studies for its potential role in testing as part of pre-treatment screening prior to the

use of trastuzumab. However, more clinical and economic evidence are needed before a concrete recommendation can be made.

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Conflict of interest

None.

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Appendix A. Supplementary data

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