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REVIEW

Genetic Polymorphisms and the Efficacy of Platinum-Based Chemotherapy: Review

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Abstract: Previous studies have indicated that genetic variations in individuals may result in changes in gene expression and amino acids. The effect of these changes may lead to different responses to platinum-based chemotherapy. A vast response rate interval and a short survival rate indicate that the efficacy and efficiency of the selection of chemotherapy have not been optimized. This article aims to illustrate the potential relationship of various genetic polymorphisms in response to platinum-based chemotherapy for several types of cancer. This review was conducted using articles from the last three- and five-year periods (2014–2019) that use gene polymorphism and its relationship to the efficacy of platinum-based chemotherapy as their theme. A total of 26 out of 488 relevant articles were included based on specific criteria. Through various mechanisms, genes, including ERCC1, ERCC2/XPD, XPC, XPA, XRCC1, APE-1, PARP1, OGG1, ABCC2, MRP, GSTP1, GSTM1, GSTT1, MATE1, and OCT2, have been associated with patient response to platinum-based chemotherapy. We conclude that genetic polymorphism analysis is recommended for the management of cancer so that each patient can be administered therapy based on his or her genetic profile to achieve an effective and efficient outcome.

Keywords: genetic polymorphism, platinum-based chemotherapy, DNA repair, drug accumulation, drug detoxification

Introduction

Platinum, in the form of cisplatin, was first approved by the FDA as a therapy for cancer in 1978. That has led to an interest in platinum or other metal-containing compounds as potential anticancer drugs.[1–3] The platinum-based chemotherapy (PBC) drugs currently prescribed include cisplatin, carboplatin, and oxaliplatin.[4] PBC has been shown to inhibit cell division in various types of cancer.[5] At sufficient intracellular levels, the drug becomes reactive and then binds to peptides and proteins containing sulfur residues such as cysteine, methionine, and especially glutathione. However, the most important therapeutic target of PBC is the DNA within the cell nucleus.[6] Platinum reacts with guanine and adenosine residues and forms a bulky-adducts. With platinum bound to the DNA, it forms a lesion and DNA crosslink. As a result, DNA transcription and replication are inhibited, resulting in the apoptosis of the cancer cells.[7] But that bulky-adducts can be recognized and repaired by the NER pathway, which requires many proteins. NER pathway causing the DNA to unwind, and platinum becomes detached. That mechanism leads to chemotherapy resistance.

Resistance is the most significant challenge to PBC's success as it can reduce or even eliminate the effectiveness of chemotherapy. Resistance occurs through several mechanisms such as increased degradation and inactivation of the drug before

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reaching its therapeutic target (nuclear DNA), decreased drug uptake into cells or increased drug efflux, increased DNA repair activity; which also includes one mechanism of DNA damage tolerance; caused by the formation of DNA adducts such as platinum–DNA adducts, and epithelial–mesenchymal transition, as well as how inherent tumor cell heterogeneity plays a role in drug resistance.[7–9] For every cellular process, there is a potential for genetic variability (individual genetics), especially in tumor somatic cells.[10] Thus, genetic changes can alter the cell phenotype and vary the response of individuals to PBC. In this review, we will discuss the mechanisms of PBC resistance associated with genetic polymorphisms.

Materials and Methods

This review summarizes the results of several studies related to the effects of polymorphisms on platinum-based chemotherapy. It includes studies from the PubMed database identified using the keywords "polymorphism," "platinum," "response," and "resistance." Articles written in a non-English language and not including PBC therapy were excluded. Moreover, manuscripts, research communications, reviews, expert opinions, and unrelated studies not associated with PBC's effectiveness were excluded (Figure 1).

A total of 488 articles were identified through the PubMed database and then limited to publications from the last three years for articles involving response and the last five years for resistance. We also filtered the list to include articles, including the term "human." As a result, the total number of articles included was 26. The majority of the articles discussed the effect of gene polymorphisms on the therapeutic outcome (side effects, effectiveness, resistance, and survival rates) from platinum-based chemotherapy in various types of cancer.

Pharmacogenetics and Its Importance

Pharmacogenetics is the study of the variability of therapeutic/drug response between individuals due to genetic variations in heredity, whereas pharmacogenomics was born as a more comprehensive study. Pharmacogenomics maps all the genetic variations, in the form of polymorphisms or mutations that have a clinical significance on

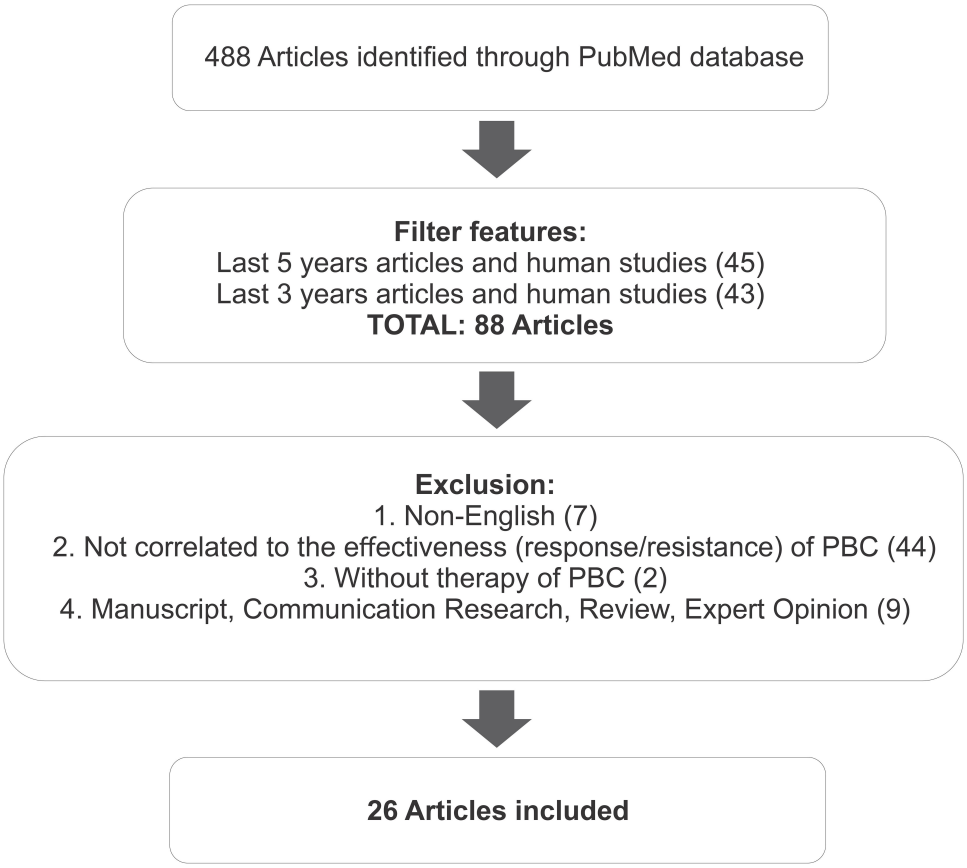

Figure 1 Flowchart depicting the literature search process.

therapeutic drug response, toxicity levels, or the incidence of resistance. Increasing our understanding of genes and completion of the Human Genome Project introduced the term of pharmacogenomics is more widely used to encompass the role of genetics in drug response.[11–13]

A mutation is a change in DNA sequences. At the same time, the term polymorphism is used to define natural variants exist for traits for which no clearly normal type can be defined and that co-exist in a population at relatively high frequencies (>1%).[14]

Pharmacogenomics is a rapidly growing field that aims to trace the interindividual-genetic differences in drug response. That study has been applied to many anticancer drugs to identify relevant inherited or acquired genetic variations that may predict patient response to chemotherapy and targeted therapies. Some of anticancer has presented variations in therapeutic response, such as in PBC, this can be seen from the overall response rate of 26–63% these variations in therapeutic response means that some of the tumors are sensitive to platinum-based, some are hypersensitive, other tumors conversely have a potentially intrinsic resistance.[15,16]

Although the efficacy of chemotherapy can be affected by many factors, genetic variation as polymorphism plays a significant role in drug response. The location or site of the polymorphism will determine the effect, like polymorphism present within a coding sequence and leading to an amino acid change (referred to as a non-synonymous SNP or mutation) can modify the protein's activity or function. If the mutation is synonymous, then translation rates or mRNA half-life may be affected. If the mutation causes a premature stop codon, this can lead to the production of a truncated protein product or nonsense-mediated decay phenotype.[17,18] So, due to differences or changes at the genetic level, causing modifications in cellular phenotype could explain some of the variability in response or toxicity.[19]

Platinum-Based Chemotherapy Resistance

Platinum-based anticancer drugs are heavily applied in chemotherapy regimens. Nevertheless, the intrinsic or acquired resistance severely limit the clinical application of platinum-based treatment. Chemotherapy resistance is the innate and/or acquired ability of cancer cells to evade chemotherapeutics' effects, and that is one of the causes of individual variation in PBC response.[20]

Previous studies on variability responses to platinum-based chemotherapy suggest that it is affected by the mechanism of how platinum is processed in the body, including pharmacokinetics and pharmacodynamics. In general, efforts have delivered evidence regarding DNA repair systems of tumor cells, and drug metabolization systems cause these variabilities in PBC response.[20,21] Chemotherapy resistance can occur through many mechanisms such as; damage in the drug delivery system, increased efflux and/or decreased drug influx, increased detoxification rate, alteration of the target site, increased damaged-DNA repair activity manifested in tolerance of DNA damage, increased anti-apoptotic factors and/or decreased pro-apoptotic factors, as well as changes in cell cycle/transcription factors.[9]

Pharmacokinetic mechanisms include a reduction in drug levels at the target site due to reduced uptake and/or increased efflux by Adenosine triphosphate-binding cassette (ABC) transporters, drug detoxication by glutathione S-transferases (GSTs), and drug elimination by Organic Cation Transporter (OCT) along with Multidrug Toxin Extrusion (MATE). It is clear that reduced drug levels at the target site will affect the formation of platinum–DNA adducts and decreases the efficacy, while alteration of elimination rate will be affected to level and severity of toxicity.[22–29] The pharmacodynamics mechanism includes increased damaged-DNA repair activity. The DNA repair mechanism's increased activity will result in failure to form DNA damage induced by platinum.[21] In contrast, tumor heterogeneity includes alteration of the target site, cell cycle stage changes, stochastic variations between tumor cells, or hierarchical organization of cells. Tumor heterogeneity is included in the intrinsic resistance factor of the tumor cells themselves.[10]

For each pharmacokinetic and pharmacodynamic mechanism, there exists the potential for genetic variabilities, such as the occurrence of polymorphisms or mutations in genes that play a role in these mechanisms. Genetic polymorphisms can modify the cell phenotype, which could explain some variabilities in the response or resistance to platinum-based chemotherapy.[21]

Nucleotide Excision Repair

Nucleotide Excision Repair (NER) is a mechanism that is directly and specifically activated when platinum-based chemotherapy is given to patients. NER mechanism is typically activated when DNA damage occurs by UV lights, environmental mutagens, and active chemotherapy substances, which cause the addition of molecules to DNA (DNA adducts), one

of which is platinum-based chemotherapy. DNA damage due to the addition of platinum is referred to as bulky lesions, while the BER repair mechanism repairs non-bulky lesions. NER is the primary mechanism of PBC resistance and is responsible for removing platinum that has been attached to the DNA of cancer cells. As a result, the repaired DNA damage prevents apoptosis from occurring (Figure 2).[31,32] The repair of DNA lesions by NER is a multistep process. It includes (a) recognizing lesions, (b) unwinding the DNA strands, (c) incision of the lesion by endonuclease activity, and (d) DNA synthesis and ligation (Figure 3). Recognition of DNA lesions may be divided into two processes: global genome repair (GGR) and transcription-coupled repair (TCR) (Figure 3). Several proteins are involved in this mechanism that affects the response to PBC (Figure 3).

Recognition of Lesion Sites

The global genomic repair (GGR) process detects lesions throughout the genome, regardless of whether a specific sequence is transcribed or not. In contrast, Transcription-Coupled Repair (TCR) is only initiated when lesions block RNA polymerases on the template of the DNA strand. Thus, these lesions are only removed from transcribed DNA sequences[33,34] (Figure 3).

Several studies have indicated that the protein responsible for initial damage recognition during GGR is xeroderma pigmentosum complementation group C (XPC).[35] This protein forms a complex with damaged DNA binding 1 and 2 (DDB1 and DDB2/XPE).[36–38] After XPC and its complex recognize the damaged site, a more stable and rigid XPC–DNA complex is formed. This complex then recruits other NER factors to the damaged site. The other NER factor that is responsible for the next step, which is the verification of the damaged DNA, is the transcription factor II H (TFIIH) complex in concert with xeroderma pigmentosum complementation group A (XPA)[39,40] (Figure 3). Verification is an essential process since XPC can only bind to DNA sites containing mismatched bases, but devoid of any lesion. To avoid an error, this process is designed to verify that a relevant lesion indeed exists. TFIIH is a complex that contains two ATPase/helicase subunits, namely, xeroderma pigmentosum complementation group B (XPB) and xeroderma pigmentosum complementation group D (XPD), and it is essential for the subsequent NER step.[41]

In TCR, the protein that plays this role is RNA polymerase II, which binds to Excision Repair Cross-Complementation group 8 (ERCC8/CSA) and Excision Repair Cross-Complementation group 6 (ERCC6/CSB) to form a complex[42] (Figure 3). A small number of mutations that occur in somatic cells can activate TCR.[43–45]

Polymorphisms that occur within genes that encode the proteins involved in the recognition step of NER, TCR, and GGR affect PBC response. A recent meta-analysis study suggests that changes in the level of XPC gene

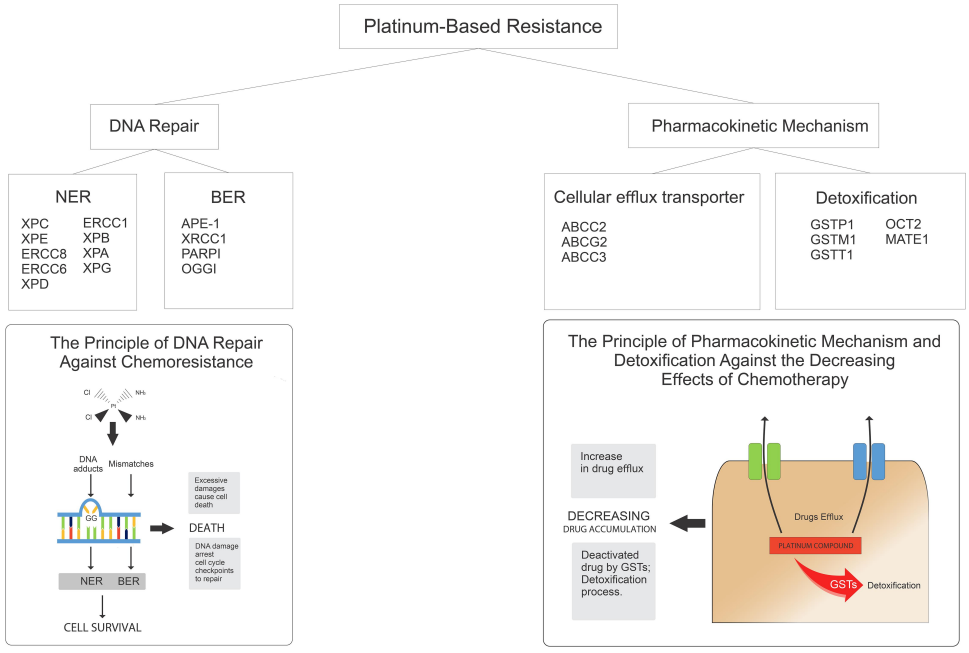

Figure 2 Principles of platinum-based chemotherapy.

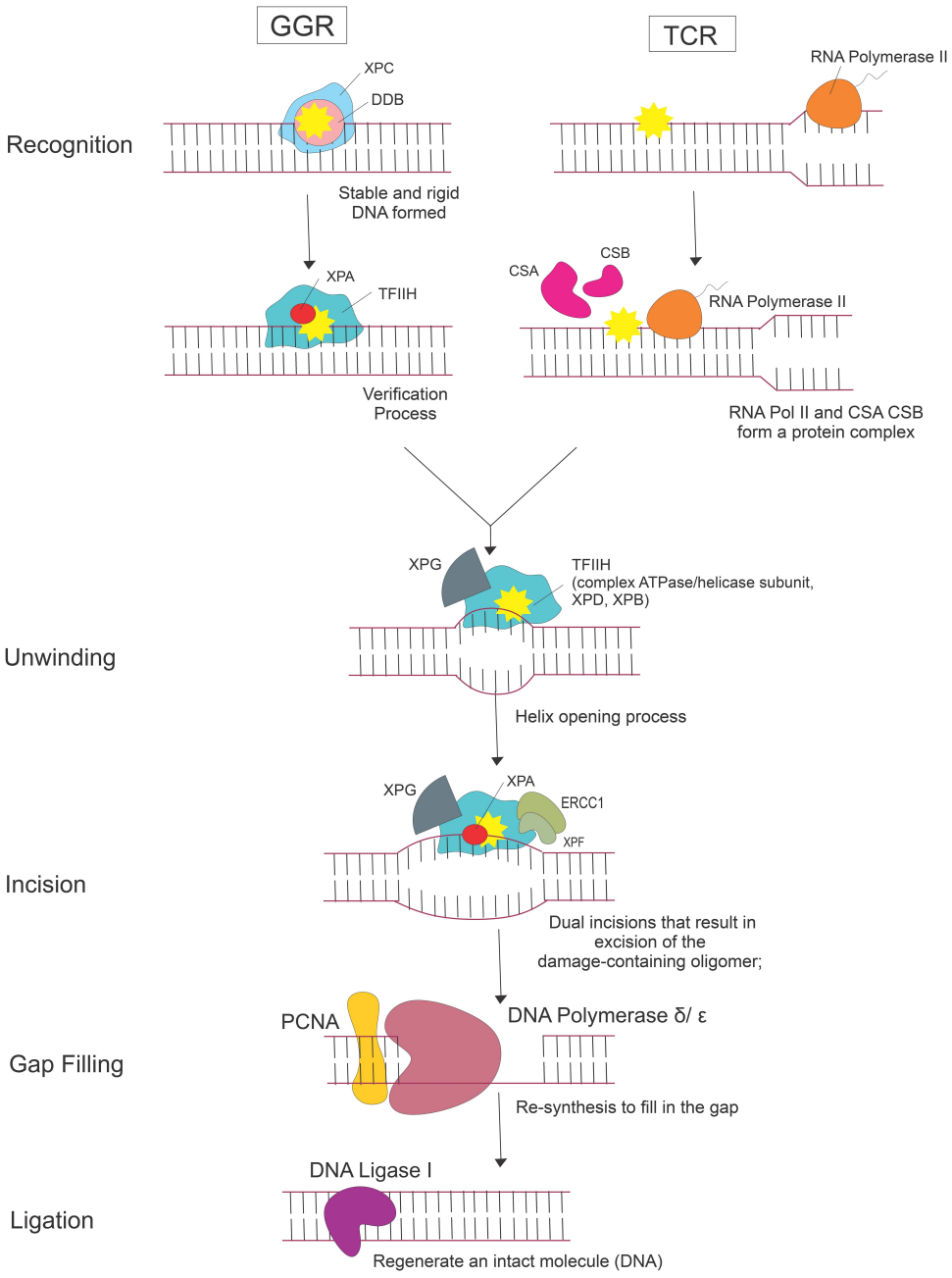

Figure 3 Nucleotide excision repair.

expression genetically predispose tumors to various PBC outcomes[46] (Table 1). Another study suggested that a polymorphism in ERCC6 could be a predictor for the clinical outcome of the platinum-based chemotherapy in Non-Small-Cell Lung Cancer (NSCLC)[47] (Table 1).

DNA Unwinding

As mentioned previously, XPD is a component of the TFIIH complex, which has a role in the DNA-unwinding process of NER.[48] Together with excision repair cross-complementation group 1 (ERCC1), the mRNA expression levels of XPD could be a predictive factor for platinum response in several types of cancer.[49] Moreover, XPB and XPA are part of the TFIIH complex. The XPA protein binds to damaged sites that have been "marked" by XPE and XPC and then unwinds the DNA in conjunction with the TFIIH complex[50,51] (Figure 3). XPA is one of the platinum efficacy predictors[52] (Table 1). Other meta-analysis studies have concluded that XPD is one of the proteins that has a significant association with PBC outcome[53] (Table 1).

Table 1 Summary of the Association of Genetic Polymorphisms to Platinum-Based Clinical Outcomes

No.	Subject	Population	Polymorphism	Results	Conclusion	Reference
1	642 patients, NSCLC	Asian	P73 G4C14-to-A4T14 (rs191470412 and rs62642520)	OS (P=0.040) GC/AT or AT/AT.	Mutant genotype has a better Overall Survival and more responsive.	[113]
2	54 patients, NSCLC	Asian	ERCC1 rs11615	OS better in wild type.	A combination of ERCC1 and ERCC2 polymorphism can be used as a predictive factor of Overall Survival	[99]
			ERCC1 rs3212986	C/C OR (48% vs 10%, P=0.005)		
			ERCC2 rs13181	Heterozygote has a better OS rather than the wild- type.		
			ERCC2 rs1799793	OS better in wild type.		
3	596 patients, Cervical Cancer.	Asian	rs6812281	Per allele OR = 2.37, P = 9.0 × 10−9,	Polymorphism can be used as a genetic etiological characterization of the NACT response of cervical cancer patients.	[114]
			rs4590782	P = 1.59 × 10−5, per allele OR = 0.48		
			rs1742101	P = 7.11 × 10−6, per allele OR = 0.52		
			rs1364121	P = 3.15 × 10−6, per allele OR = 1.98		
4	26 articles, NSCLC	Asian and Caucasian	14 SNPs from 8 genes	XPD (rs1799793); ERCC1 (rs3212986); XPA (rs1800975); ERCC1 (rs3212948); XRCC1(rs25487); XRCC3(rs861539); APE1(rs3136820); ERCC1 (rs11615); XRCC1(rs1799782); RRM1(rs1042858); XPD (rs13181); XPG (rs1047768); XPG (rs17655); XRCC1(rs25489).	The best predictor factor for evaluating the efficacy of PBC in the NSCLC is ERCC1(rs11615), XRCC1(rs25487, rs1799782) and XPD (rs13181).	[52]
5	1004 patients, Pulmonary cancer	Asian	173 SNPs from 27 genes	ERCC5 rs2296147 has a RR significance	This study suggests that SNPs in the NER pathway could be potential predictors for clinical outcomes of platinum-based chemotherapy among NSCLC.	[47]
				GTF2H4 rs3218804 against clinical benefit is significant.		
				POLD2 rs3757843, XPA rs3176658, ERCC6 rs12571445 and POLE rs11609456, rs5744751 significant in PFS.		
				GTF2H4 rs3130780, GTF2HA rs3130780, MAT1 rs4151374, POLD1 rs2546551 significant in OS.		

(*Continued*)

Table 1 (Continued).

No.	Subject	Population	Polymorphism	Results	Conclusion	Reference
6	111 Articles, NSCLC	Caucasian and Asian	11 SNP from 9 genes	ERCC1 rs11615 (OS), rs3212986 (ORR), XPA rs1800975 (ORR), XPD rs1052555 (OS, PFS), rs13181 (OS, PFS), XPG rs2296147 (OS), XRCC1 rs1799782 (ORR), XRCC3 rs861539 (ORR), GSTP1 rs1695 (ORR), MTHFR rs1801133 (ORR), and MDR1 rs1045642 (ORR).	DNA Repair; (EXCC1, XPA, XPD, XPG, XRCC1 and XRCC3), Medicine Influx/efflux; (MDR1), Metabolism and Detoxification; (GSTP1), DNA synthesize; (MTHFR).	[53]
7	241 Patients, Pulmonary cancer.	Caucasian	XRCC1 rs25487	Mutant genotype has a better Survival (MST = 9.6).	Polymorphism of XRCC1 have an impact on OS	[115]
			XRCC1 rs3547	In SCLC, mutant genotype increasing Death Rate (HR 3.08, p = 0.02).		
8	31 Articles NSCLC.	Caucasian and Asian	GSTP1 rs1695	GSTP1 Ile105Val Ile/Val and Val/Val (Asia) (odds ratio (OR) = 1.592, 95% confidence intervals (CIs), 1.087–2.332, P = 0.017).	Polymorphism of GSTP1 Ile105Val, GSTM1 GSTT1 null genotype could be a predictive factor for PBC's efficacy.	[89]
			GSTM1 rs366631	GSTM1 null genotype (Asian) (OR = 1.493 (1.192–1.870), P < 0.001)		
			GSTT1 rs17856199	GSTT1 null genotype (Caucasian) (hazard ratio (HR)= 1.423, CI=1.084–1.869, P= 0.011)		
9	13 Articles, Gastric cancer.	Caucasian and Asian	ERCC2 rs13181	No significance association against OS nor PFS	Polymorphism of ERCC2 rs1799793 could be a predictor factor of PBC's efficacy.	[100]
			ERCC2 rs1799793	In Asian, there is a significant association (AA vs GG: HR=1.77, 95% CI, 1.20–2.6; GA +AA vs GG: HR = 1.62, 95% CI, 1.26–2.09), but negative result means no significance association in Caucasian.		
10	43 Patients, Squamous Cancer, Adenocarcinoma	Caucasian	ERCC1 rs11664579	TT genotype in ERCC1 and GT genotype in MDR1; PFS (p = 0.006 and p = 0.027 respectively).	The expression of ERCC1 could be a predictor for prognosis and survival. While over-expression of III β-tubulin related to chemo-resistance.	[116]
			MDR1 rs2032582			
			III β-tubulin	High III beta-tubulin expression was associated with chemotherapy resistance and fewer responses [5/20 (25%)]		

(*Continued*)

Table 1 (Continued).

No.	Subject	Population	Polymorphism	Results	Conclusion	Reference
11	19 Articles, NSCLC.	Caucasian and Asian	XRCC1 rs25487	OS (GlnGln + GlnArg vs ArgArg: HR = 0.65(95% CI: 0.43–0.98)) PFS (GlnGln vs ArgArg: HR = 0. 72(95% CI: 0.48–0.97)) in Asian. In Caucasian; OS (GlnGln vs ArgArg: HR = 2.29 (95% CI: 1.25–3.33)).	In Caucasian, polymorphism rs25487 has worse OS. In contrast, Asians have better PFS. Polymorphism of rs1799782 has a worse response.	[74]
			XRCC1 rs1799782	(ArgArg vs TrpTrp: OR = 0.64 (95% CI: 0.44–0.91); ArgArg + TrpArg vs TrpTrp: OR = 0.79(95% CI: 0.57–1.11); TrpArg vs TrpTrp: OR = 1.05(95% CI: 0.73–1.51)).		
12	370 Patients, Pulmonary Cancer.	Caucasian	XPD rs13181	CC genotype against risk factor (p = 0.01).	rs13181 and rs1799793 could be a predictor factor for clinical response.	[117]
			XPD rs238406	CC genotype against Median survival time = 25.2		
			XPD rs1799793	GA against worsening survival (P=0.01)		
13	12 Articles, NSCLC	Caucasian and Asia	XPG rs17655	In Asian; (GG vs CC: OR = 1.57, 95% CI: 1.05–2.34, P=0.027).	No strong evidence about XPG's polymorphism that could be a predictor factor.	[118]
			XPG rs1047768	No significant association to RR and OS.		
14	170 Patients, NSCLC.	Caucasian	ABCC2 rs8187710	Adverse OS (Adjusted hazard ratio [aHR] 2.22; 95% CI: 1.2–4.0; p = 0.009)	rs8187710 (4544G>A), have association to OS.	[29]
15	103 Patients, Gastric Cancer	Asian	ABCC2 rs717620	TT and TC genotype have a better response of chemotherapy 3.80 times than CC genotype (95% CI: 1.27–11.32).	Polymorphism of ABCC2-24C > T could be a clinical predictor factor of Platinum-Based Chemotherapy.	[81]
16	129 Patients, NSCLC	Asian	ABCG2 rs2725264	(OS) (P=0.018, Log rank test);	ABCG2 rs2725264 and rs4148149 polymorphism related to OS.	[82]
			ABCG2 rs4148149	OS (P = 0.014, Log rank test);		
17	142 Patients, NSCLC	Asian	BAG-1 rs11551682	CT genotype has a sensitivity 0.383 times better than CC (P< 0.05).	Polymorphism combination of BAG-1 and XPD could be a marker of the sensitivity of Platinum-Based Chemotherapy.	[119]
			XPD rs13181	Lys/Gln have a sensitivity 0.4 times better than Lys/Lys (P<0.05)		
			XPD rs1799793	Asp/Asp combined with Lys/Lys (rs rs13181) and CT (rs11551682), has better efficacy and rather than the mutant type (P< 0.005).		

(*Continued*)

Table 1 (Continued).

No.	Subject	Population	Polymorphism	Results	Conclusion	Reference
18	8 Articles, Ovary Cancer	Caucasian and Asia	ERCC1 rs11615	OR (C vs T alleles) is 1.07 (95% CI 0.75–1.52, P = 0.7), means no significance.	No association with the efficacy of Platinum-Based Chemotherapy.	[120]
19	152 Patients, NSCLC	Asian	PARP1 rs1136410	CC ([OR]: 5.216, 95% confidence interval [CI]: 1.568–17.352, P = 0.007), TC (OR: 2.692, 95% CI: 1.007–7.198, P = 0.048), TC + CC (OR: 3.178, 95% CI: 1.229–8.219, P = 0.017)	Alleles mutant C have an association to decreasing sensitivity of Platinum Based Chemotherapy.	[121]
20	84 Patients, NSCLC	Asian	GSTP1 rs1695	AG + GG have a better and significance survival time than AA (P<0.05),	Polymorphism of GSTP1 rs1695 and ABCC2 rs717620 could be a clinical outcome factor of PBC.	[88]
			ABCC2 rs717620	CT + TT has a better significance in survival time than CC (P<0.05).		
21	29 Articles, NSCLC	Caucasian and Asia	XRCC1 rs1799782	TT vs CC [OR 1.65 (1.29-2.10)], P= <0.01	Polymorphism of XRCC1 Arg194Trp is related to PBC's efficacy.	[122]
			XRCC1 rs25487	AA vs GG [OR 1.11 (0.68-1.82)], P=0.70		
22	39 Articles and 1024 Patients, NSCLC	Caucasian and Asia	XRCC1 rs25487	GA/GG vs AA [(OR = 0.72, 95% CI: 0.53–0.96, P = 0.028; Meta-analysis: OR = 0.74, 95% CI: 0.62–0.89, P = 0.001)].	XRCC1 G1196A/C580T and XRCC3 C18067T could be a basis for individual therapy.	[91]
			XRCC1 rs1799782	CT/TT have a better sensitivity than CC (OR = 0.54, 95% CI: 0.37–0.80, P = 0.002).		
			XRCC3 rs861539	CC more resistance than CT/TT (OR = 0.69, 95% CI: 0.52–0.91, P = 0.009).		
23	235 Patients, NSCLC	Asian	BCL2 rs2279115	CA+AA [hazard ratio (HR) 1.456, p=0.009];	This research shows that both polymorphisms could be a predictor factor of the clinical outcome of Platinum-Based Chemotherapy.	[123]
			BAX rs4645878	GA+AA have a worse response [odds ratio (OR) 1.943, p = 0.039; OR 1.867, p = 0.038, respectively]. HR 1.506, p = 0.003		

(*Continued*)

Table 1 (Continued).

No.	Subject	Population	Polymorphism	Results	Conclusion	Reference
24	28 Patients, Ovary Cancer	Caucasian	Nup107 rs79419059	Association with platinum resistance (P = 0.0061); (odds ratio: 4.519, 95% confidence interval: 1.317–15.501, P = 0.0457).	3′-UTR region of Nup107 related to platinum resistance and could be a predictor factor of Platinum-Based Chemotherapy's response.	[124]
			Nup188 rs2302811	Association with platinum resistance (P = 0.0483 and 0.0091, respectively).		
			Nup214 rs77246077			
25	91 Patients, NSCLC	Caucasian	RRM1 rs12806698	AA have a significance association with better PFS 10.5 vs 3.5 months, p = 0.0437; HR = 2.17, 95% CI 1.02–4.62. CC [OS (9.5 vs 18 months, p = 0.0193; HR = 2.13, 95% CI 1.13–4.03)].	Polymorphism of RRM1 genes could be a predictor factor of PBC-Gemcitabine combination.	[125]
			RRM1 rs11030813	CC have a significance association with better PFS PFS 10.5 vs 3.5 months, p = 0.0343; HR = (2.12, 95% CI 1.06–4.27).		
26	403 Patients, NSCLC	Asian	OCT2 rs316019	Association with hepatotoxicity (P = 0.026) and hematology toxicity (P=0.039)	OCT2 rs316019, MATE1 rs2289669, and ABCC2 rs717620 could be a clinical marker, toxicity, and PBC response.	[93]
			MATE1 rs2289669	Hematology toxicity (P=0.016)		
			ABCC2 rs717620	The response of platinum's efficacy (P=0.031)		
			ABCB1 rs1045642	No association to response or toxicity		

Abbreviations: NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; OS, overall survival; OR, odds ratio; ORR, overall response rate; PFS, progression-free survival; HR, hazard ratio; RR, relative risk; Gln, glutamine; Arg, arginine; Val, valine; Trp, tryptophan; Lys, lysine; Asp, aspartic acid.

Incision of the Lesion

ERCC1 is a protein that plays a major role in platinum resistance in recent years.[49] ERCC1 forms heterodimers with XPF and is involved in the process of DNA incision[54] (Figure 3). In vitro studies have indicated that a decrease in regulation or double knockdown of the XPF-ERCC1 complex increases the efficacy of cisplatin.[55] Results from Phase II clinical studies indicate that the level of ERCC1 mRNA expression of ERCC1 is a predictor of PBC response.[56] The International Adjuvant Lung Cancer Trial Biologic Program (IALT-Bio) states that ERCC1 is a biomarker for determining chemotherapy selection.[57] In other types of cancer, the role of ERCC1 as a predictive factor remains unclear. Another protein that plays a role in the incision step and has a significant association with PBC outcome is XPG/ERCC5[53] (Table 1). The final step in the NER process is gap filling and ligation, which is conducted by several proteins, including DNA polymerase, PCNA, and DNA ligase (Figure 3).

Base Excision Repair

Base excision repair (BER) plays a role in removing non-helical-distorting bases or non-bulky DNA lesions from the genome that arise from alkylation, deamination, or oxidation. Some of the alkylating agents are exogenous agents contained in food; such as nitrosamines (cigarettes

and food with intensive thermal treatment),[58,59] alkylating agents found in the environment from industry and agriculture; such as vinyl chloride, which is used as a raw material in the plastics industry, bromomethane fumigants from the agricultural industry, and chloromethane, which is used as a coolant.[60–63] Several other alkylating agents, including cyclophosphamide, melphalan, busulfan, and temozolomide, are widely used in chemotherapy.[64,65] The deamination of a DNA base can occur spontaneously[66,67] because of inflammation, which results in oxidative deamination, or can be produced enzymatically.[68–70] Whereas base oxidations occurwhen DNA bases interact with reactive oxygen species (ROS) formed by ionizing radiation or produced under physiological conditions.

There are two types of BER in mammals. Short-Patch (SP) is a mechanism for single-nucleotide replacement, and Long-Patch (LP) replaces 2 to 13 nucleotides. The protein component of these BER mechanisms includes glycosylase, endonuclease, DNA polymerase, and DNA ligase (Figure 4). Therefore, the genes that express those proteins are considered as a predictor of chemosensitivity.[71]

As listed in Table 1, the ERCC1 polymorphisms, namely, Arg194Trp and Arg399Gln, are considered predictors of chemotherapeutic drug sensitivity. In studies of an Asian population, a relationship between increased PBC sensitivity in patients with these polymorphisms was evident.[72,73] Moreover, other studies have reported

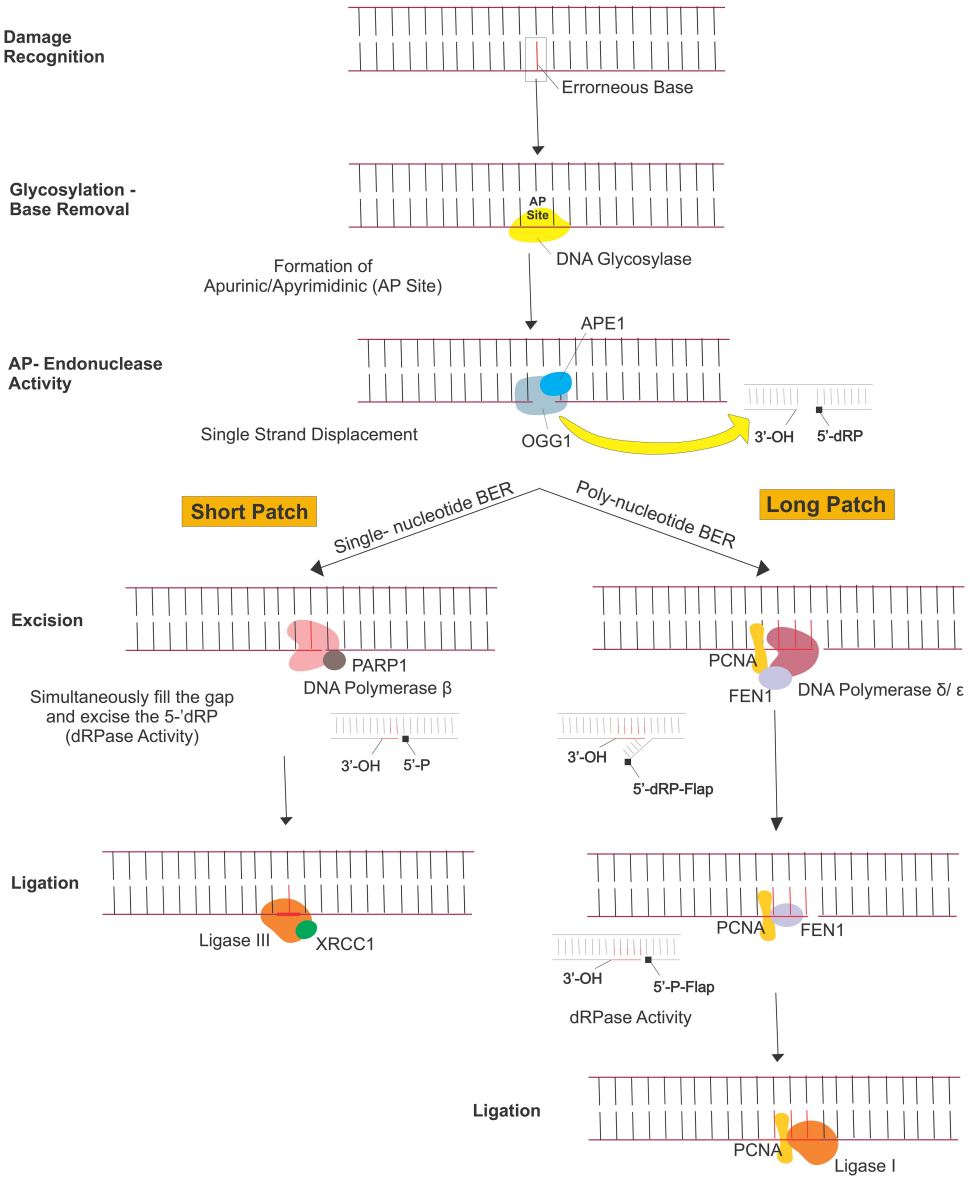

Figure 4 Base excision repair.

that the XRCC1 rs25487 polymorphism results in a worse overall survival in a Caucasian patient cohort. Although the PFS in the Asian population was longer, the XRCC1 rs1799782 polymorphism produces a worse objective response.[74] In addition to XRCC1, the other genes that play a role in the BER mechanism include APE-1, PARP1, and OGG1. These three genes are associated with PBC's clinical outcomes and decreased PFS in patients who express variant alleles.[75]

Pharmacokinetic Mechanism

One mechanism of PBC resistance is decreased intracellular drug accumulation, which prevents the drug from reaching its target.[76] The causes of the decreased drug accumulation include inhibition of drug uptake, increased drug efflux, or a combination of both. Another mechanism at this pharmacokinetic stage is the process of drug detoxication. The proteins which are critical players in the metabolism of many chemotherapeutic agents and play a role in the mechanism of reducing drug accumulation include the Adenosine triphosphate-binding cassette transporter family and proteins that play a role in the detoxication process, such as glutathione S-transferase, organic cation transporter, and multidrug toxin extrusion.[25,28,29,77,78]

Adenosine Triphosphate-Binding Cassette Transporter Family

Adenosine triphosphate-binding cassette (ABC) transporters, including ABCB, ABCC, and ABCG, represent general biological defenses against environmental toxicants. ABC transporters are an example of ATP-dependent pumps, and they can move substrates in (influx) or out (efflux) of cells. For example, such proteins play a role in increasing the efflux of hydrophobic cytotoxic drugs. These proteins utilize the energy derived from ATP hydrolysis to transport both endogenous and exogenous substances through the cell membrane.[19,79] ABCC2 is a protein known to play a role in the transport of glutathione-conjugated platinum out of cells. ABCC2 was shown in in vitro studies to represent a mechanism leading to platinum-based chemotherapy resistance.[19,25,80] As listed in Table 1, an ABCC2 polymorphism is associated with the overall survival of patients with advanced-stage NSCLC.[29] A polymorphism in ABCC2 (rs717620) resulting from an alteration of C to T is known to be related to neoadjuvant chemotherapy's pathological response. Another study has indicated that this protein is related to the tumor regression grade (TRG) value.[81]

ABCG2 htSNP rs2725264 may be independently associated with OS in unresectable NSCLC patients treated with first-line platinum-based chemotherapy.[82] A study of the rs4148416 polymorphism of ABCC3, another member of the multidrug resistance protein (MRP) family, showed that this polymorphism was associated with a low survival rate.[83]

Detoxication Process

Platinum-containing drugs can be deactivated by glutathione S-transferases (GSTs). These enzymes, categorized as phase II metabolic enzymes, GSTs catalyze the conjugation of glutathione (GSH) to platinum. The formation of platinum–glutathione inactivates the drug by increasing its solubility that leading to excretion.[84] Variations in GSTs have implications for cellular resistance to PBC. When GST enzyme activity decreases, the drug concentration within the tumor tissue increases and causes an increased risk of platinum toxicity.[26] There are two families of GST enzymes involved in cisplatin detoxification; GSTP1 and GSTM.[24,27] Besides GSTs, several other proteins affect the detoxication process.

Glutathione S-transferase P1 (GSTP1) is expressed in epithelial cells. Polymorphisms in the GSTP1 gene, such as the A to G base change in rs1695, cause the conversion of isoleucine to valine. This polymorphism results in the reduced activity of the GSTP1 enzyme and loss of this gene's alleles causes the complete loss of enzymatic activity.[85,86] Other studies suggest that polymorphisms at these sites are associated more with changes in PBC toxicity, such as granulocytopenia and peripheral neuropathy induced by platinum.[86,87] Several recent studies showed that the GSTP1 polymorphism represents a predictive factor for the outcome of NSCLC patients treated with PBC[88] (Table 1). Data from a meta-analysis showed that the Asian GSTP1 genotype, IIe105Val IIe/Val and Val/Val, exhibited a better response compared with IIe/IIe[89] (Table 1). Furthermore, the GSTM1 polymorphism with a "null" phenotype is associated with a better response to PBC in Asian lung cancer patients. A meta-analysis regarding glutathione indicated that the GSTP1 polymorphism, IIe105Val, as well as the GSTM1 and GSTT1 null variants, may be useful predictors for the effectiveness of PBC[89] (Table 1).

Elimination Process

Besides GSTs enzymes, summarized in Table 1, some transporters can affect the detoxification rate and implicated to the clinical outcome of PBC, include organic cation transporter 2 (OCT2) and multidrug toxin extrusion 1 (MATE1).

Platinum is eliminated through the proximal tubule of the kidney.[90] OCT proteins are expressed in the kidney. Thus, they have an essential role in the regulation of platinum distribution and excretion.[28,91] At the same time, MATE1 is an H^+-coupled organic cation exporter expressed on the luminal membrane and renal duct.[77,78] It is involved in excretion, specifically in the renal tubules.[92] Both proteins are related to the disposition of platinum.[30] The results of one study indicated that the polymorphisms, namely, OCT2 r316019 and MATE1 rs2289669, OCT2 rs316019, were associated with hepatotoxicity (P = 0.026) and hematological toxicity (P = 0.039), and MATE1 rs2289669 was associated with hematological toxicity induced by platinum (P = 0.016). Both of OCT2 and MATE1 are potential clinical markers for the toxicity of PBC in NSCLC.[93]

Discussion

This study aims to review several studies related to the correlation of gene polymorphisms to the efficacy of platinum-based chemotherapy in several types of cancer. The majority of studies were subjects with lung cancer (especially NSCLC), cervical, gastric, and ovarian cancer. From a total of 26 articles (original research and meta-analysis) included in the inclusion, there is the variability of the study results. The variation in the results of each study referred to the statistical significance of the results, the value and interpretation of the correlation, and the incidence rate of the polymorphism itself.

Polymorphism is defined as natural variants that exist for traits for which no clearly normal type can be defined and co-exist in a population at relatively high frequencies (>1%).[14] In the human genome, any two randomly chosen DNA molecules are likely to differ at about one SNP site every 1000 base pair (bp) in noncoding DNA and at about one SNP site every 3000 bp in protein-coding DNA. SNPs are the most common form of genetic differences among people. About 3 million SNPs that are relatively common in the human population have been identified,[94] and The effects of the variant form may be both beneficial and detrimental, depending on the circumstances.

SNPs not just responsible for the disease but also other clinical manifestations such as therapeutic outcomes or drug resistance that do not necessarily have to occur in coding regions. They could occur in any genetic region that can affect the expression, structure or form, or activity of the protein. SNPs in genetic regions like transcription factor binding domains, promoter regions, intron-exon boundaries, may cause defects in splicing or mRNA signal process.[95]

For a long time, it has been known that genetic variation, including SNPs, is influenced by many factors, one of which is race/ethnicity. The studies that were included in this review show a different result between Asian and Caucasian. However, it is known that even in the same races/population, the incidence of genetic variability between individuals also has a high probability.[96] Therefore, genetic-related studies, even in the same race, may have different results. This is what underlies a systematic review, review studies, and meta-analysis of genetic polymorphism urgently needed.

As in this article, the result of polymorphism analysis against chemotherapy response studies in patients with different cancer types was linear. As in NSCLC, lung cancer in general, and gastric cancer, ERCC2 rs1799793, the mutant genotype will have worse chemotherapy efficacy with shorter survival. Whereas in NSCLC and gastric cancer, ABCC2 rs717620, the mutant genotype had better survival and response.

ERCC2 or XPD is a gene that encodes the XPD protein, which is a component of the transcription factor complex II H (TFIIH) and has ATP-Dependent Helicase activity. In other words, the XPD protein is included as a helicase enzyme and plays a vital role in the DNA repair mechanism.[97,98] Amino acid changes due to A>C polymorphism (rs1799793) affect the alteration of activity and function of these proteins. The impact of these changes is related to the clinical outcome of chemotherapy's effectiveness, such as decreased response and survival.[99,100] In contrast to ABCC2, which is one of the MRP transporter families that encodes Multidrug Resistance-associated Protein 2, it functions as an organic anion transporter, playing a role in platinum-conjugated transport out of cells. C>T polymorphisms (rs717620) are associated with altered ABCC2 expression or function. Besides promoting the export of glutathione-conjugated platinum, upregulated ABCC2 expression also decreases the formation of platinum-DNA adducts and reduces G2-arrest in cisplatin-resistant cell lines. This polymorphism's clinical

manifestation is an increase in the response of platinum-based chemotherapy survival rates.[101–103]

However, in this review, we found the contradictory result between the studies, as in XRCC1 rs1799782, where the mutant genotype is known to have low overall survival. In contrast, the results of other studies suggest that the mutant genotype has a better chemotherapy response. It is influenced by several factors, one of which is the amount of data (sample subjects or articles) that are different. Several studies, with a smaller number of data samples, become their limitations and affect reliability. Meanwhile, factors other than polymorphism also play an important role related to chemotherapy response, such as tumor heterogeneity, age, comorbidity and severity, treatment modality, previous therapy response, stage, serum albumin levels, the general condition of patients on Zubrod and Karnofsky scales, histology, and types of cancer, as well as chemotherapy side effects that occur in patients.[104–108]

Age is related to physiology and comorbidities. A study stated that patients under 60 years old had a higher chance of survival with p = 0.016.[104] Meanwhile, research in Japan concluded that the level of serum albumin and patient comorbidity (Charlson Comorbidity Index) are fundamental factors in the clinical response of elderly patients over 75 years.[105] Other studies stated that comorbidity and their severity could affect the chemotherapy response. Studies conducted on breast cancer patients proved this with OR = 0.46; 95% (CI: 0.27–-0.76) among patients with a Charlson score of 2 versus 0.[107] In a meta-analysis study, it was stated that in general, the response to chemotherapy could differ between types of cancer and their histology. It is also greatly influenced by choice of chemotherapy regimen and stage.[108]

Conclusion and Prospects

Polymorphisms that occur in several genes related to DNA repair or a drug's pharmacokinetic mechanism in cancer patients may involve the alteration of one base with or without a significant clinical impact. The effects of such changes are related to the gene coding instructions, such as at the level of gene expression, or the amount and type of amino acids produced. It is directly or indirectly results in a different response for each individual to platinum-based chemotherapy. Treatment management based on gene polymorphisms is not new, but it has been used thus far for metastatic cancer patients to identify gene polymorphisms related to targeted drug therapy.[109] For several cancers, polymorphism detection is used as a preventive measurement, assessment, or risk factor for cancer.[110–112] Our review demonstrates that the examination of genetic profiles that influence the efficacy of chemotherapy is highly recommended. It will be beneficial as a consideration for the selection of the type of chemotherapy regimen to achieve cost-effective and efficient therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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