

# Genetic Navigation: A Narrative Review of XRCC1 Polymorphism Impact on Platinum-Based Chemotherapy Outcomes in NSCLC Patients

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**Abstract:** Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 85% of all cases, with a poor 5-year survival rate of less than 20%. The majority of NSCLC patients are diagnosed at an advanced stage, contributing to the low survival rate. Platinum-based chemotherapy, including cisplatin and carboplatin, remains the cornerstone of treatment for advanced NSCLC. However, DNA repair mechanisms often hinder treatment efficacy, notably Base Excision Repair (BER), mediated by the X-ray Repair Cross Complementing 1 (XRCC1) protein. This review aims to investigate the role of *XRCC1* polymorphisms in platinum resistance, focusing on their impact on DNA repair efficiency. *XRCC1*'s involvement in the BER pathway is critical for repairing DNA damage caused by platinum agents, and polymorphisms in *XRCC1* have been linked to altered repair capacity, influencing clinical outcomes and resistance to platinum-based chemotherapy in NSCLC patients.

**Keywords:** non-small cell lung cancer, DNA repair, base excision repair, *XRCC1* polymorphism, platinum-based chemotherapy, response therapy, toxicity, survival rates, Platinum-based

## Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer worldwide, comprising approximately 85% of all reported cases.<sup>1,2</sup> Globally, the 5-year survival rate for NSCLC is less than 20%.<sup>3</sup> Most NSCLC patients are diagnosed at an advanced stage (70%), contributing to the low overall survival rate.<sup>4-6</sup> Although local data from Indonesia are limited, this pattern reflects universal challenges in managing NSCLC across populations. Platinum-based chemotherapy, such as cisplatin and carboplatin, remains the mainstay of treatment for advanced NSCLC.<sup>7-9</sup> Platinum compounds enter cancer cells via passive transport mediated by Copper Transporter 1 (CTR1)<sup>10</sup> and direct passive diffusion across the cell membrane,<sup>11</sup> then damage DNA. However, the efficacy of platinum agents is often hampered by resistance caused by DNA repair mechanisms such as Base Excision Repair (BER).<sup>12</sup>

The BER pathway, mediated by the XRCC1 protein, plays a critical role in repairing DNA damage and ensuring the survival of cancer cells.<sup>12</sup> XRCC1 coordinates repair by recruiting DNA glycosylase, AP-1 enzyme (APE-1), Poly (ADP-ribose) polymerase 1 (PARP-1), DNA polymerase Beta (Pol-β), and DNA Ligase III (LIG-3) to the site of damage.<sup>12,13</sup> Genetic variations in *XRCC1* can affect protein functionality and DNA repair capacity, thereby affecting the efficacy of platinum chemotherapy. Polymorphisms on XRCC1, such as rs1799782 and rs25487, have been associated with different therapeutic responses, making them candidate biomarkers for predicting treatment outcomes.<sup>14,15</sup>

Based on data from PharmGKB, the level of evidence for the rs25487 variant is at level 2B (a combination of variant-drug with moderate evidence supporting the association) in the efficacy of platinum compounds,<sup>16</sup> while the rs1799782 variant is at level 3.<sup>17</sup> Global data shows that the frequency of the *XRCC1* variant allele is around 20%,<sup>18,19</sup> so it is anticipated that variant alleles with a similar frequency (>20%) are also present in the Indonesian population.<sup>20</sup> This

article aims to comprehensively examine the impact of XRCC1 gene polymorphism on the outcomes of platinum-based therapy in influencing DNA repair capacity. Variants of XRCC1 such as rs25487, rs1799782, and rs25489 are associated with diverse clinical outcomes, including chemotherapy response, toxicity profiles, and overall survival (OS) progression-free survival (PFS) rates. Consequently, the review further evaluates the clinical implications and future directions of NSCLC treatment, investigating the potential of precision medicine in disease management. This article aims to comprehensively review the role of XRCC1 polymorphisms in platinum resistance and their potential application in the precision medicine of NSCLC.

## Platinum Therapy in NSCLC

Platinum-based chemotherapy is the frontline treatment option for NSCLC patients, particularly those with Epidermal Growth Factor Receptor (*EGFR*) and Anaplastic Lymphoma Kinase (*ALK*) negative tumor mutations.<sup>7-9</sup> Platinum inhibits Deoxyribonucleic Acid (DNA) replication in the nucleus, providing a practical cytotoxic effect on cancer cells.<sup>21,22</sup> At the molecular level, platinum agents form DNA adducts, either mono-adducts or intra- or interstrand adducts. These interactions involve covalent bonds that cause DNA lesions and cross-links between DNA strands, inhibiting cancer cell replication. Accumulation of DNA damage occurs in the G2/M phase, which ultimately triggers apoptosis of cancer cells.<sup>23</sup> Platinum agents such as cisplatin and carboplatin show similar mechanisms of action. Cisplatin, with two amine groups (-NH<sub>3</sub>) and two chloride atoms (Cl<sup>-</sup>), and carboplatin, with a 1,1-cyclobutane dicarboxylate (CBDCA) ring, undergo hydrolysis reactions in the cell cytoplasm. This reaction replaces the Cl<sup>-</sup> atom or CBDCA ring with a water molecule (H<sub>2</sub>O), making platinum agents highly reactive. Platinum binds to the nitrogen atom (N) at position N7 in the DNA's purine ring (adenine and guanine). This bond causes DNA damage, inhibits DNA synthesis, and ultimately triggers apoptosis.<sup>24,25</sup>

NSCLC cancer cells generally show sensitivity to platinum agents due to their tendency to have high proliferation rates and often inefficient DNA repair mechanisms.<sup>26</sup> This makes them susceptible to platinum-induced DNA damage. However, the use of platinum agents faces several limitations. In addition to high levels of toxicity that can affect patients' quality of life, platinum's effectiveness often decreases over time.<sup>27</sup> One of the main resistance mechanisms is the activation of DNA repair pathways, especially the BER pathway. The BER pathway allows cancer cells to repair DNA damage caused by platinum agents, thereby reducing the cytotoxic effects of these agents.

## Base Excision Repair (BER) Pathway

The BER pathway is a type of DNA repair activated in response to minor problems such as base damage due to oxidation, deamination, or alkylation.<sup>28</sup> DNA repair is essential for repairing errors during DNA replication or damage caused by radiation, chemicals, or metabolic byproducts. In normal cells, this DNA repair helps protect and maintain the integrity of the genetic material.<sup>29,30</sup> However, in cancer cells, this pathway may provide a selective advantage by helping cancer cells repair DNA damage induced by platinum-based therapies, thereby increasing resistance to chemotherapy.

The BER process begins with the identification of DNA lesions by DNA glycosylases, such as Human 8-oxo guanine DNA glycosylase 1 (hOGG1), which removes the damaged nucleotide base, leaving behind an apurinic/apyrimidine site (AP site). Next, the APE-1 cleaves the DNA strand near the AP site, creating a gap with a free phosphate group at the 5' end and a hydroxyl group at the 3' end.<sup>31</sup> Next, DNA POL-β fills the DNA gap created by APE-1. POL-β exhibits dual enzymatic activities: deoxyribose phosphodiesterase (dRPase) activity removes the residual sugar-phosphate group at the 5' end of the DNA gap, and DNA polymerase activity adds a new nucleotide at the 3' end, elongating the DNA strand and repairing the missing gap. After filling the gap, LIG-3 closes the DNA gap by forming a phosphodiester bond between the 3'-OH and 5'-phosphate ends. LIG-3 works in a complex with XRCC1. Throughout the BER process, XRCC1 acts as a scaffolding protein that regulates enzyme interactions and ensures that repair occurs quickly and accurately.<sup>31</sup>

## XRCC1 Protein: Role, Mechanisms, and Interaction

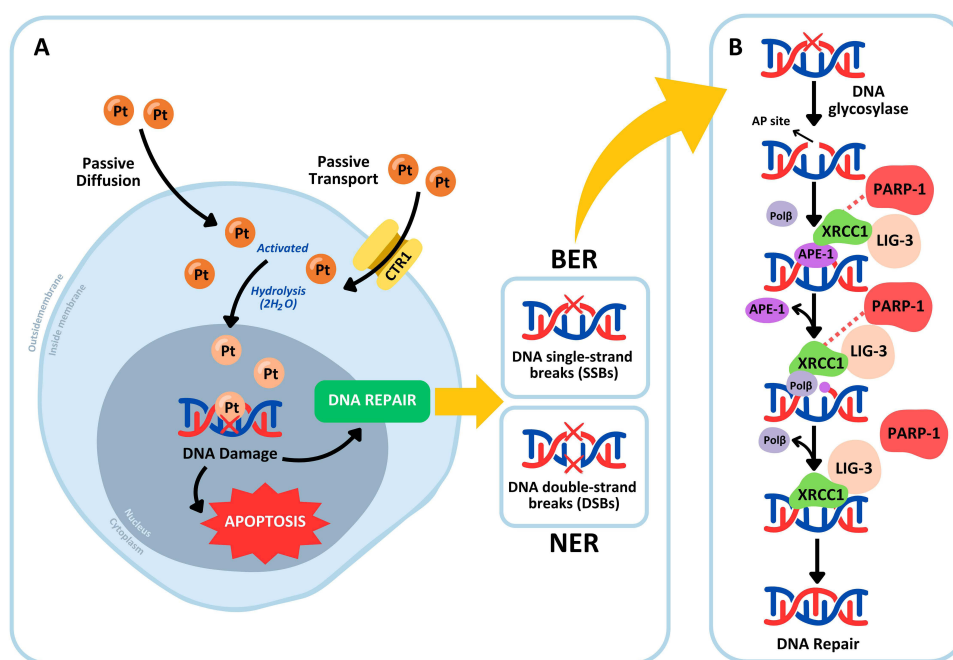
XRCC1 is a protein encoded by the *XRCC1* gene, functioning as a key organizer in the BER pathway.<sup>32,33</sup> Deficiency or absence of this protein can result in inefficient DNA repair, accumulation of DNA damage, and increased risk of various

diseases.<sup>34,35</sup> XRCC1 works with PARP-1 to coordinate subsequent steps in the repair process, including the activities of POL- $\beta$  and LIG-3. PARP-1 is an essential enzyme for detecting DNA damage, especially single-strand breaks (SSBs).<sup>33</sup> Upon recognizing damage, PARP-1 initiates ADP-ribosylation, marking the site of damage with the PARP-1 chain. This serves as a recruitment signal for DNA repair proteins, including XRCC1. PARP-1 activation facilitates chromatin relaxation around the damage site, allowing XRCC1 and other enzymes to access the damaged DNA.<sup>36,37</sup>

In addition to aiding recruitment, XRCC1 prevents excessive PARP-1 activity, which can lead to DNA structural entrapment during repair and trigger additional damage.<sup>37</sup> The interaction between XRCC1 and PARP-1 is critical for XRCC1 function during BER. Loss of PARP-1 function can impair XRCC1 recruitment, while XRCC1 deficiency can result in excessive PARP-1 activity, leading to an imbalance in the BER pathway.<sup>37</sup> Early in the repair process, XRCC1 interacts with hOGG1 and APE-1 at unstructured junctional regions.<sup>38</sup> This interaction ensures the transfer of DNA substrates from hOGG1 (which generates AP sites) to APE1 (which cleaves AP sites to continue the repair process). This coordination is critical for efficiency and avoids the formation of toxic intermediates that can cause additional DNA damage.<sup>39</sup> XRCC1 also interacts with DNA by binding to its ends at SSB sites, stabilizing POL- $\beta$  during the gap-filling step, and supporting LIG-3 in rejoining DNA strands. Its ability to physically interact with the enzymes involved (such as hOGG1, APE1, POL- $\beta$ , and LIG-3) makes it a key component in regulating DNA repair (Figure 1).<sup>39–43</sup> XRCC1 dysfunction or genetic mutations affecting this protein have been associated with resistance to platinum-based therapy in NSCLC.

## XRCC1 Variants

As previously explained, the presence of the XRCC1 protein is the key to the success of the BER pathway DNA repair process. Deficiency or absence of this protein will disrupt the DNA repair process. The XRCC1 protein is encoded by the *XRCC1* gene, which is located on chromosome 19q13.2. This gene consists of 17 exons that encode a protein consisting of 633 amino acids<sup>41</sup> and has three main domains: the N-terminal domain (NTD) that interacts with Pol- $\beta$ ,<sup>42</sup> the BRCT1 domain involved in interactions with PARP-1 and DNA,<sup>31,40</sup> and the BRCT2 domain that interacts with LIG-3.<sup>43</sup> In addition, the linker region facilitates interactions with proteins such as hOGG1 and APE-1.<sup>39</sup>



**Figure 1** Mechanism of Platinum-Induced DNA Damage and BER Pathways in Cancer Cells. (A) Platinum (Pt) enters cells through passive diffusion and CTR1-mediated transport, causing DNA damage. Repair mechanisms, including base excision repair (BER) and nucleotide excision repair (NER), address single-strand breaks (SSBs) and double-strand breaks (DSBs). Persistent DNA damage leads to apoptosis. (B) BER Pathway Mechanism: DNA glycosylase removes damaged bases in BER, creating an AP site cleaved by APE-1. XRCC1 orchestrates repair by recruiting Pol $\beta$ , LIG-3, and PARP-1, restoring DNA integrity after SSBs.

Studies on *XRCC1* polymorphisms indicate that this genetic variation can affect DNA repair capacity. Previous studies have mainly focused on three SNP variants: rs25487, rs1799782, and rs25489. In the rs25487 variant, the polymorphism occurs in exon 10 at codon 399, which is located in the BRCT1 domain region, the binding site for PARP-1.<sup>41,44</sup> The presence of polymorphism in this region produces a missense variant characterized by a base change from guanine (G) to adenine (A), leading to the substitution of the amino acid arginine (Arg) for glutamine (Gln).<sup>45,46</sup> These changes may affect the interaction between XRCC1 and the PARP-1 enzyme. This interaction begins with transferring a covalent bond from the nicotinamide adenine dinucleotide (NAD<sup>+</sup>) molecule to the ADP-ribose polymer chain by the PARP enzyme. The bond formation involves the amine group (-NH<sub>3</sub>) of arginine and the polymer chain of ADP-ribose.<sup>47</sup> Furthermore, this interaction induces PARP-1 activation at the DNA strand break site, facilitates damage recognition, and participates in the repair process.<sup>48</sup> The rs25487 variant, which replaces arginine with glutamine, reduces the reactivity of the amine group (-NH<sub>3</sub>) on the glutamine residue to ADP-ribose. As a result, covalent bond formation is disrupted, dimming the interaction between XRCC1 and PARP-1. This reduced interaction hurts DNA repair capacity.<sup>37</sup> Studies have reported similar findings confirming that decreased XRCC1-PAPR-1 interaction correlates with reduced DNA repair efficiency.<sup>37</sup>

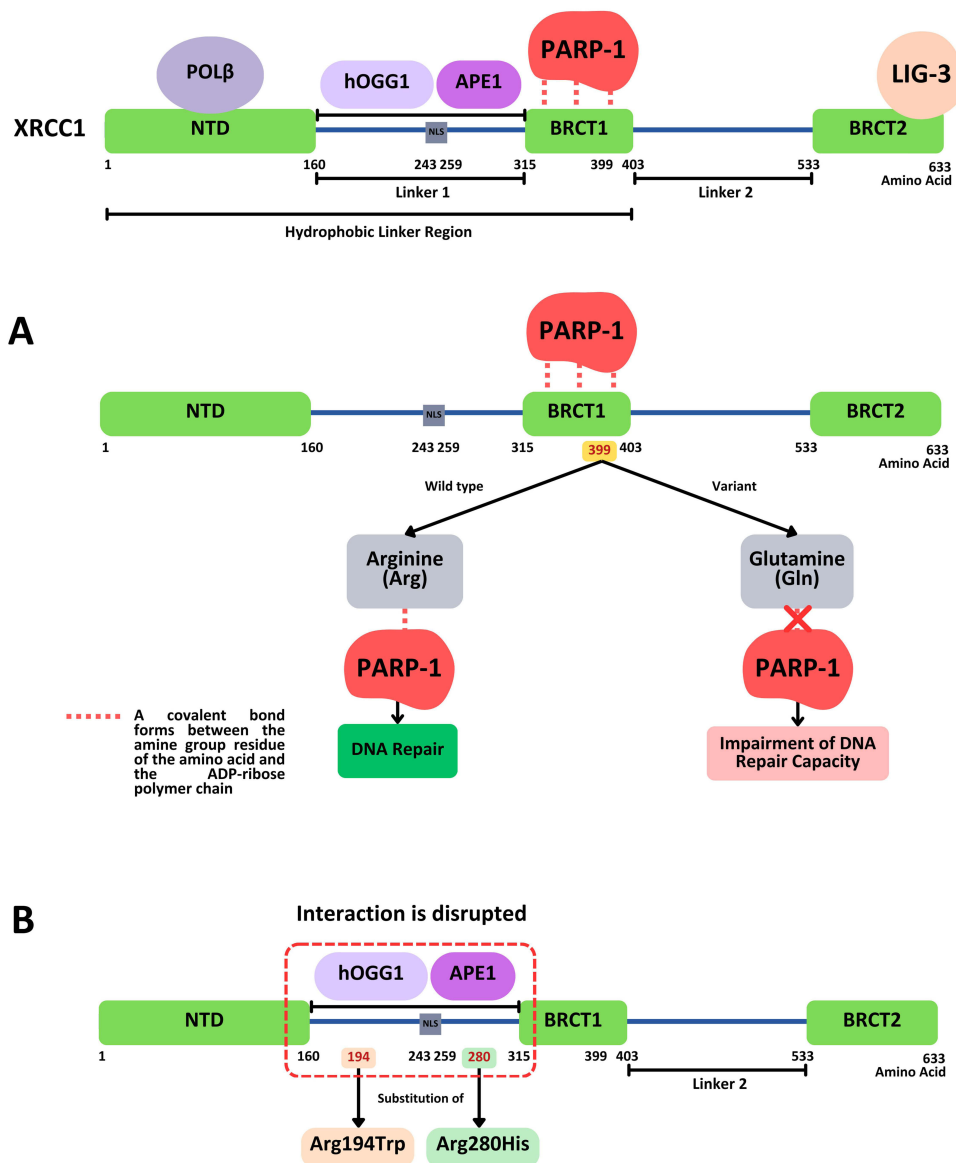
Another polymorphism, namely the rs1799782 variant, occurs in exon six at codon 194,<sup>41</sup> and also has a missense variation due to a base change from cytosine (C) to thymine (T); this leads to the replacement of arginine (Arg) with tryptophan (Trp) within the unstructured linker region. This substitution disrupts the interaction of XRCC1 with hOGG1, which is important for recruiting XRCC1 to sites of oxidative DNA damage (such as 8-oxoG).<sup>38</sup> In addition, this variant has been reported to fail to recruit LIG-3 to the BER site, potentially interfering with subsequent steps of DNA repair.<sup>38</sup> Besides rs1799782, another variation in the unstructured linker region is rs25489, located in exon nine at codon 280.<sup>41</sup> This variant involves a base substitution from guanine (G) to adenine (A), resulting in arginine (Arg) being substituted for histidine (His).<sup>41</sup> This region serves as the interaction site between XRCC1 and the APE-1 enzyme. Since XRCC1 has no enzymatic or catalytic activity, its interaction with other proteins, such as APE-1, relies entirely on direct physical interactions. This polymorphism affects the affinity of XRCC1 for APE-1, with amino acid changes, resulting in decreased XRCC1 binding affinity and the ability to interact with the APE-1 protein.<sup>49</sup> Overall, all three polymorphism variations lead to a decrease or reduction in the interaction of XRCC1 with enzymes involved in DNA repair, which ultimately reduces the capacity of the BER pathway DNA repair and is associated with resistance and increased toxicity of platinum-based chemotherapy in NSCLC patients (Figure 2). In addition to the above variants, there is a variant of rs3213239 insertion/deletion type whose data is still very limited (Table 1).<sup>50</sup>

## XRCC1 Polymorphism to The Clinical Outcomes of Platinum-Based Chemotherapy in NSCLC

XRCC1 protein plays an essential role in enhancing DNA repair capacity in the BER pathway, which is responsible for repairing DNA damage caused by oxidative stress and alkylating agents, including platinum-based drugs such as cisplatin and carboplatin. Genetic variations in *XRCC1*, such as at positions Arg194Trp, Arg280His, or Arg399Gln, can alter the efficiency of the DNA repair process, affecting the accumulation of DNA damage in cells. This accumulation determines the effectiveness of therapy in inducing cancer cell death and can also affect toxicity to normal tissues.<sup>26</sup> Therefore, understanding the impact of *XRCC1* polymorphisms is essential for predicting clinical outcomes, including response rate to treatment, toxicity, overall survival, and progression-free survival in lung cancer patients (Table 2).

## Responses

*XRCC1* gene polymorphisms have been extensively studied to determine their effect on platinum-based chemotherapy response in NSCLC patients across populations. For example, a study in Bangladesh showed that patients with the Arg/Gln (G/A) variant or Gln/Gln (A/A) variant had a better therapeutic response to platinum-based chemotherapy (OR = 2.40; 95% CI = 1.21–4.76; p = 0.012).<sup>51</sup> Similar results were found in studies of South Korean and Chinese populations, where the Gln/Gln (A/A) variant was associated with a higher response rate.<sup>15,52–55,69</sup> However, these results are not uniform across populations. Studies in Greek and Spanish populations did not find a significant association between the rs25487 variant and



**Figure 2** XRCC1 coding region. XRCC1 interacts with several proteins participating in DNA repair processes, such as DNA polymerase beta (Pol $\beta$ ), Human 8-oxoguanine DNA glycosylase I (hOGG1), and AP endonuclease I (APE1). NTD: N-Terminal Domain; NLS: Nuclear Localization Signal; BRCT1/2: BRCA1 Carboxy-terminal domain. **(A)** Polymorphism of XRCC1 Arg399Gln. The amino acid change from Arg to Gln can disrupt DNA repair capacity. **(B)** Polymorphism of XRCC1 Arg194Trp and Arg280His in Linker 1 region.

response to platinum-based chemotherapy.<sup>50,56</sup> In contrast, other studies reported that the Gln/Gln variant decreased the response to platinum therapy in NSCLC patients.<sup>14,57</sup> These differences in results are likely due to different genetic frequency distributions in each population and other factors such as sample size and genetic background.<sup>29,55,58</sup>

**Table 1** Polymorphism on XRCC1 Genes

Genes	dbSNP	Alleles	Types	Reference
XRCC1	rs25487	G $\rightarrow$ A	Missense	[14,29,51–64]
	rs1799782	C $\rightarrow$ T	Missense	[15,50,54,55,58,59,61,65,66]
	rs25489	G $\rightarrow$ A	Missense	[50,55,59,61]
	Rs3213239	GGCCGGCCG $\rightarrow$ GGCCG	Insertion/Deletion	[50]

**Table 2** The Study of XRCC1 Polymorphisms on Clinical Response to Platinum-Based Chemotherapy in NSCLC Patients

No.	Study	Year	Country	Sample Size	Polymorphism			Result and Conclusion	
					Genotyping Method	SNPs	Mutation	Outcomes	Statistic Value
1	Tiwari et al <sup>60</sup>	2022	India	52	PCR-RFLP	rs25487	G>A	Variants AA and GA+AA have been associated with significant hematological toxicity.	OR= 16.33; 95% CI= 2.66–100.26; p= 0.003 and OR: 5.20; 95% CI= 1.15–23.83; p= 0.031
2	Bushra et al <sup>51</sup>	2020	Bangladesh	285	PCR-RFLP	rs25487	G>A	Variants AA and GA+AA have been associated with significantly better response. Variants AA and GA+AA have been associated with significant hematological toxicity.	OR= 2.40; 95% CI= 1.21–4.76; p= 0.012 p= 0.008; p= 0.010; p= 0.025; and p= 0.002
3	Dong et al <sup>29</sup>	2018	China	152	PCR MALDI-TOF	rs25487	G>A	No significant association was found with response.	p= 0.180
4	Bu et al <sup>54</sup>	2016	China	141	PCR-RFLP	rs25487 rs1799782	G>A C>T	Variant AA has been associated with significantly better response. No significant association.	OR= 2.71; 95% CI= 1.13–10.08; p= 0.01 p= 0.34
5	Liu et al <sup>53</sup>	2015	China	322	PCR-RFLP	rs25487 rs1799782	G>A C>T	Variant AA has been associated with significantly better response. Variants AA and GA have been associated with a significantly decreased risk of death. No significant association.	OR= 3.37; 95% CI= 1.44–8.53; p= 0.002 HR= 0.53; 95% CI= 0.31–0.91; p= 0.01 and HR= 0.39; 95% CI= 0.18–0.83; p= 0.006 p= 0.09
6	Powro'zek et al <sup>67</sup>	2015	Polandia	55	PCR	rs25487	A>G	A-allele has been associated with significantly lower hematological toxicity after 4th cycle.	OR= 0.22; 95% CI= 0.06–0.82; p= 0.018
7	Zhao et al <sup>59</sup>	2015	China	206	PCR-RFLP	rs25487 rs1799782 rs25489	G>A C>T G>A	No significant association. Variant TT has been associated with significantly better response and lower risk of death. No significant association.	OR= 3.23; 95% CI= 1.20–9.30; p= 0.01 and HR= 0.05; 95% CI= 0.01–0.18; p= <0.001
8	Jin et al <sup>55</sup>	2014	China	378	PCR-RFLP	rs25487 rs1799782 rs25489	G>A C>T G>A	Variant AA has been significant association with a better response and longer Disease-Free Survival (DFS) and Overall Survival (OS). No significant association. No significant association.	OR= 2.27; 95% CI= 1.64–6.97; p= <0.05; and HR= 0.47; 95% CI= 0.22–0.82; p= <0.05; and HR= 0.52; 95% CI= 0.31–0.96; p= <0.05



9	Peng et al <sup>68</sup>	2014	China	235	PCR-CTTP	rs25487	G>A	Variant GA or AA has been a significantly higher of grade 3–4 hematologic toxicity and increased risk of hematology toxicity.	OR= 1.852; 95% CI= 1.019–3.363, p= 0.029 and adjusted OR= 2.135; 95% CI= 1.207–3.777; p= 0.009
10	Sullivan et al <sup>50</sup>	2014	Spain	161	RT-PCR	rs25487 rs1799782 rs25489	G>A C>T G>A	No significant association. No significant association. No significant association.	p= 0.482 p= 0.467 p= 0.125
11	Zhang et al <sup>15</sup>	2014	China	375	PCR	rs25487 rs1799782	G>A C>T	Variant AA has been a significant association with a better response and lower risk of death. No significant association.	OR=1.97; 95% CI= 1.05–3.84; p= <0.05 and HR= 0.55; 95% CI= 0.23–0.94 p= 0.78
12	Lee et al <sup>69</sup>	2013	South Korea	382	PCR-RFLP	rs25487	G>A	Variant AA has been a significant association with a worse response.	OR= 3.92; 95% CI= 1.37–11.21; p= 0.01
13	Tiseo et al <sup>63</sup>	2013	Italy	110	RT-PCR	rs25487	G>A	Variant AA has been a significant association with an increased OS.	HR= 0.47; CI 95%= 0.23–0.95; p=0.036
14	Zhao et al <sup>52</sup>	2013	China	147	RT-PCR	rs25487	G>A	Variant AA+AG has been a significant association with a better response.	OR= 2.35; 95% CI= 1.11–5.00
15	Ke et al <sup>58</sup>	2012	China	460	PCR-CTTP	rs25487 rs1799782	G>A C>T	Variant AA has been a significant longer survival time and lowered the risk of death. Variant TT has a significantly decreased risk of death.	HR= 0.42; 95% CI=0.21–0.82 HR= 0.45; 95% CI= 0.23–0.87
16	Li et al <sup>14</sup>	2012	China	89	PCR	rs25487	G>A	Variant GG has a higher response rate than A allele.	OR= 4.81; 95% CI= 1.778–13.013; p= 0.002
17	Dong et al <sup>70</sup>	2011	China	568	TaqMan	rs25487	G>A	Variant AA has been significantly associated with death.	HR= 1.66; 95% CI= 1.08–2.55
18	Liu et al <sup>65</sup>	2011	China	199	PCR-RFLP	rs3213245	T>C	No significant association (OS and PFS).	p= 0.399 and p= 0.763
19	Zhou et al <sup>57</sup>	2011	China	116	PCR	rs25487	G>A	Variant GG has a higher response rate than GA+AA.	p= 0.005
20	Yuan et al <sup>61</sup>	2010	China	199	PCR-RFLP	rs25487 rs1799782 rs25489	G>A C>T G>A	No significant association. No significant association. No significant association.	

(Continued)

**Table 2** (Continued).

No.	Study	Year	Country	Sample Size	Polymorphism			Result and Conclusion	
					Genotyping Method	SNPs	Mutation	Outcomes	Statistic Value
21	Kalikaki et al <sup>56</sup>	2009	Yunani	119	PCR-RFLP	rs25487	G>A	Variant AA has been a significantly associated with OS. No significant association found with a better response.	HR= 3.1; 95% CI= 1.4–6.8; p= 0.005 p= 0.66
22	Sun et al <sup>66</sup>	2009	China	82	RT-PCR	rs25487 rs1799782	G>A C>T	No significant association. Variant CC has been a significantly associated with better response.	p= 0.997 p=0.035
23	Yao et al <sup>71</sup>	2009	China	108	PCR-RFLP	rs25487	G>A	No significant association.	p= 0.50
24	Wang et al <sup>72</sup>	2008	China	116	PCR-RFLP	rs25487 rs1799782	G>A C>T	Variant GA+AA have been significantly associated with overall grade toxicity and increased risk of grade 3 or 4 gastrointestinal toxicity. No significant association.	OR= 2.05; 95% CI= 1.02–4.10; p= 0.04 and OR= 2.53; 95% CI= 1.06–6.03; p= 0.03 p= 0.64
25	Gianchio et al <sup>62</sup>	2007	Italy	203	PCR-RFLP	rs25487	G>A	Variant A/A had a significant association with better survival in patients with grade toxicity (3 or 4).	HR= 0.46; CI 95%= 0.22–0.98





Meta-analysis and bioinformatics provide additional insights. A meta-analysis concluded that the rs25487 variant had no significant association with response to platinum-based chemotherapy.<sup>73</sup> Bioinformatics analysis also showed that the rs25487 variant was predicted to be “benign” and did not significantly interfere with protein function. In contrast, the rs1799782 variant showed a low sorting intolerant from tolerant (SIFT) score (0.01–0.04), indicating a detrimental impact on XRCC1 protein function.<sup>73</sup>

In the rs1799782 variant, patients with the Trp/Trp (T/T) variant were significantly associated with a better response (OR = 3.23; 95% CI = 1.20–9.30;  $p = 0.01$ ).<sup>59</sup> A meta-analysis reported polymorphisms in the rs1799782 variant identified from 1145 among 2926 lung cancer patients, stating that patients with the Arg/Trp (C/T) and Trp/Trp (T/T) variants tended to have a good response (OR, 2.54; 95% CI, 1.95–3.31;  $p = 0.590$ ).<sup>74</sup> This was confirmed by seven studies including 1208 patients in the Asian population, where the Arg/Arg (C/C) genotype was associated with a worse response in those receiving platinum-based chemotherapy (OR = 0.55; 95% CI: 0.36–0.84;  $p = 0.013$ ).<sup>74</sup> Furthermore, the results of an analysis comparing 2228 NSCLC patients from nine studies reported a preference for the T allele variant in achieving a complete or partial response (OR = 1.38; 95% CI: 1.16–1.65;  $p < 0.001$ ; I<sup>2</sup> = 25.5%).<sup>75</sup> A possible mechanism to explain how the rs1799782 variant can protect platinum resistance is the disruption of the interaction between XRCC1 and enzymes involved in repair.<sup>38</sup>

## Toxicities

Platinum-based chemotherapy, such as cisplatin and carboplatin, is known to have high toxicity.<sup>76</sup> Cisplatin often causes emesis, nephrotoxicity, and neurotoxicity. Meanwhile, carboplatin is more likely to cause hematological toxicity due to its myelosuppressive effects.<sup>77,78</sup> A study of the *XRCC1* rs25487 polymorphism reported that this variant could be used as a predictive factor for platinum-based chemotherapy toxicity, such as grade 3 and 4 anemia ( $p = 0.008$ ), neutropenia ( $p = 0.010$ ), thrombocytopenia ( $p = 0.025$ ), along with gastrointestinal toxicity ( $p = 0.002$ ).<sup>51</sup> Another study reported that the Gln/Gln (A/A) variant carries a 16-fold higher risk (OR: 16.33, 95% CI: 2.66–100.26,  $P = 0.003$ ).<sup>60</sup> Adjusted logistic regression analysis gender, age, smoking status, disease stage, histopathology, Eastern Cooperative Oncology Group (ECOG) stage, and chemotherapy regimen showed a significantly higher incidence of grade 3–4 hematologic toxicity in those with Arg/Gln (G/A) or Gln/Gln (A/A) variants.<sup>60</sup> Decreased DNA repair activity in *XRCC1* variants is believed to be the primary cause of this increased toxicity. Platinum-based chemotherapy damages DNA, both in cancer and healthy cells. The inability to repair DNA damage in normal cells can exacerbate the side effects experienced by patients.<sup>79</sup>

## Overall Survival (OS) and Progression-Free Survival (PFS)

DNA repair capacity in the BER pathway is critical in maintaining genome stability. Under normal conditions, low BER capacity increases the risk of cancer development due to the inability to repair DNA damage, resulting in cellular mutations that can drive tumor growth. Conversely, high BER capacity makes tumor cells more resistant to DNA-based therapies like platinum-based chemotherapy.<sup>80</sup>

Several studies have linked *XRCC1* polymorphisms to survival in NSCLC patients.<sup>15,52,53,55,58</sup> For example, the rs25487 polymorphism was reported to prolong OS and decrease the risk of death in patients with the Gln/Gln (A/A) or Arg/Gln (G/A) genotypes.<sup>53</sup> These results are consistent with previous studies showing that the rs25487 polymorphism prolongs OS and reduces the risk of death in NSCLC patients.<sup>15,59</sup> Similar results were found in the rs1799782 polymorphism, where patients with the Trp/Trp (T/T) variant showed a lower risk of death and longer OS.<sup>58</sup>

The difference in outcomes based on ethnicity is also highlighted. In the Asian population, Gln/Gln (A/A) variant in rs25487 was associated with better OS and PFS (Hazard Ratio (HR) = 0.65; 95% CI 0.43–0.98 and HR = 0.67; 95% CI 0.40–0.94), whereas in the Caucasian population, the same variant was associated with worse outcome (HR = 2.29; 95% CI 1.25–3.33).<sup>74</sup> Furthermore, the Trp/Trp (T/T) variant in rs1799782 polymorphism contributed to longer OS in NSCLC patients (HR = 0.63,  $p = 0.013$ ).<sup>75</sup> Yuan et al (2010) conducted a haplotype study for the rs1799782, rs25487, and rs25489 variants in the Chinese population, the results of which showed that the Trp/Arg/Arg (T/G/G) haplotype has the potential to protect against death (OS) compared to the reference (Arg/Arg/Arg).<sup>61</sup>

## Challenges and Limitations

Clinical implementation of *XRCCI* polymorphism research results faces several challenges. Genetic testing and interpretation complexity is a significant obstacle, especially in diverse populations. Variability in the reporting of genetic data can lead to differences in interpretation, thus affecting treatment decisions.<sup>74,75</sup> Further investigation in the broader population is needed to reduce bias and develop universally accepted clinical guidelines. In addition, integrating *XRCCI* genotyping into clinical practice requires training for healthcare workers, especially in oncology, to ensure accurate and meaningful genetic interpretation. Logistical factors, such as the availability of sophisticated genetic testing facilities, also pose challenges to widespread adoption.<sup>81</sup>

Regarding the cost perspective, the expenses associated with genetic testing pose a significant barrier. Therefore, it is essential to consider the financial implications for healthcare institutions and patients, as genetic testing may not always be covered by insurance or accessible to individuals with limited reports. Addressing the cost-effectiveness of *XRCCI* genotyping is crucial to ensuring equitable access to this precision method. Furthermore, ethical considerations are necessary because patient consent, privacy, and the responsible use of genetic information are essential. Clear protocols for obtaining informed consent and safeguarding patient data must be established to uphold ethical standards.

## Conclusion

In conclusion, this review shows the significance of *XRCCI* polymorphism in influencing treatment outcomes among NSCLC patients receiving platinum-based chemotherapy. Understanding genetic variations in *XRCCI* offers potential for precision treatment methods. However, challenges related to genetic testing complexity, interpretation, cost, and ethical considerations must be addressed to maximize the clinical utility of *XRCCI* genotyping. The potential of targeted therapies designed explicitly for *XRCCI* variants presents an exciting avenue for improving treatment efficacy and outcomes in NSCLC patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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