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ORIGINAL RESEARCH

Exploring Genetic Variants and Platinum Chemotherapy Response in Indonesian Non-Small Cell Lung Cancer Patients: Insights from *ERCC2* rs13181

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Purpose: Individual responses to platinum-based treatment for Non-Small Cell Lung Cancer (NSCLC) are influenced by genetic polymorphisms, including Single Nucleotide Polymorphisms (SNPs). This study aimed to explore the role of ERCC2 in the Nucleotide Excision Repair (NER) pathway for platinum-based chemotherapy in NSCLC. While *ERCC2* is widely studied, data for Southeast Asian populations are lacking. Addressing this gap could improve personalized treatment strategies for NSCLC in this demographic.

Patients and Methods: This study recruited 82 NSCLC patients with wildtype mutations of *EGFR* at Dr. H.A. Rotinsulu Lung Hospital, Bandung, and Dharmais Cancer Hospital, Jakarta. Data were collected prospectively from whole blood samples and medical records, while the effectiveness of chemotherapy was assessed by evaluating the response using RECIST 1.1 criteria on fourth cycle of chemotherapy.

Results: The results of this study showed the presence of genotype variation among the subjects, with frequency distribution as follows: AA genotype (82.9%), AC genotype (15.9%), and CC genotype (1.2%). The analysis of the association between *ERCC2* rs13181 CC + AC versus AA with RECIST 1.1 yielded an odds ratio (OR) of 1.042 (95% CI: 0.292–3.715; p=0.950). A multivariate analysis that included cancer stage and chemotherapy regimen as additional variables produced an adjusted odds ratio (aOR) of 0.970 (95% CI: 0.263–3.568; p=0.963).

Conclusion: This study did not find statistically significant associations between *ERCC2* rs13181 polymorphisms and chemotherapy responses. However, this research highlights the presence of genetic variation within the Indonesian population, with the AA genotype being the most prevalent, which may influence chemotherapy responses. The results provided preliminary data and lay the foundation for future comprehensive cohort observational investigations.

Keywords: ERCC2, genetic polymorphism, Indonesia, RECIST 1.1, platinum-based

Introduction

Cancer is the second leading cause of death worldwide, accounting for approximately one in six deaths in 2018.[1] The incidence of new lung cancer cases in Indonesia has increased more than fivefold over the past decade, with the majority (85%) being Non-Small Cell Lung Cancer (NSCLC).[2,3] This condition has low survival rates, with a first, second, and third-year overall survival rate of 94%, 91%, and 78% respectively.[4] The 5-year survival rate is only 24% with one of the contributing factors being delayed diagnosis and treatment.[5,6] Statistical data show that 65% of NSCLC cases are

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diagnosed at an advanced stage,[3,7] leading to delayed initiation of treatment. Meanwhile, platinum-based (PB) chemotherapy is known to have variability in effectiveness, with an overall response rate (ORR) ranging from 26% to 63%.[6,8] Studies in the UK have reported rates of 20% to 40%, while a pooled analysis yielded an ORR range of 29.7% to 46.7% for PB regimens.[9,10] This has evolved into a significant concern, given that PB treatment protocols are integrated into the national healthcare coverage and persist as the predominant choice for initial therapy among Indonesian NSCLC patients with wildtype *Epidermal Growth Factor Receptor* (*EGFR*) profile.[3] Targeted therapies including Vascular Endothelial Growth Factor (VEGF) inhibitors, bevacizumab, or ALK-inhibitors namely crizotinib for ALK and c-ros oncogene 1 (ROS1)-positive mutations, as well as immunotherapy (atezolizumab) for those with high Programmed Death-Ligand 1 (PD-L1) expression, are not currently provided by the national healthcare coverage.[11–16] The widespread use of PB regimens in Indonesia is in contrast to the potential benefits associated with biologic agents, which are generally regarded as more effective for NSCLC treatment whether used individually or in combination.[14]

In the context of platinum-based chemotherapy response, genetic factors, particularly single nucleotide polymorphisms (SNPs), play a crucial role in influencing treatment response. These genetic markers, which impact either the pharmacodynamics (PD) or pharmacokinetics (PK) of the drug, are essential for understanding the variability in patient outcomes. While PK-related genes are involved in the Absorption, Distribution, Metabolism, Excretion (ADME), or detoxification pathways, PD-related genes are associated with the platinum's mechanism of action, particularly in DNA repair processes like nucleotide excision repair (NER) and base excision repair (BER). Variations in these genes can alter the activity of DNA repair pathways, which play a key role in tolerating the DNA damage caused by the formation of platinum-DNA adducts.[17] Furthermore, polymorphism associated with NER and BER genes, including *Excision Repair Cross-Complementing group 1/2* (*ERCC1*/*ERCC2*), and *X-ray repair cross-complementing protein 1/2/3* (*XRCC1/2/3*), have been identified in several meta-analysis as the best factors related to alteration of sensitivity to PB chemotherapy,[18–20] while *Xeroderma Pigmentosum Group A-Complementing Protein* (*XPA*) polymorphism have been associated with clinical benefit.[21] From The Clinical Pharmacogenetics Implementation Consortium (CPIC) lists five genes, including *ERCC1*, as having a D evidence level, and one gene, *MTHFR*, as having a C evidence level. According to PharmGKB data, *ERCC1*, *ERCC2*, *XPC*, and *XRCC1* are listed at level 3. This information indicates that these genetic markers, particularly *ERCC1* and *ERCC2*, which have been the primary focus of previous studies evaluating individual responses to platinum-based chemotherapy in NSCLC, are key markers in the NER pathway. In addition to being known for its association with chemotherapy response, *ERCC2* rs13181 polymorphism is also recognized for its significant sensitivity to ethnicity/race.[20,22,23] This issue becomes crucial as we enter the era of precision medicine. The lack of global genetic diversity in research limits the applicability of biomedical findings across different ethnicities and populations. Most human genomics studies have focused on individuals of European ancestry, who represent only a small fraction of the global population.[24–26] However, they currently have weak evidence for use in pharmacogenetic screening.[18,27–31] This is largely due to the limited number of studies on this topic, especially those conducted in developing countries.[32–34] Additionally, no studies have yet investigated the relationship between *ERCC2* and the clinical response to platinum-based chemotherapy in Indonesia.[29]

Another equally important fact is Indonesia has significant genetic diversity, largely influenced by the history of archaic humans. This diversity drives variation in gene regulation within the Indonesian population, including variations inherited from archaic humans such as Denisovans and Neanderthals. These factors contribute to a unique genetic architecture in Indonesia, impacting how genes are regulated and expressed in this population.[35] Recent meta-analysis of 121 eligible studies found that subgroup analysis by ethnicity for *ERCC1* rs11615 indicated an increased risk of platinum-based chemotherapy resistance in Asians across all genetic models examined, while for *ERCC2* rs13181, Asians had a higher odds ratio (OR) compared to Europeans, suggesting that population stratification contributes to the high heterogeneity observed. The confounding effect of ethnicity is apparent, as *ERCC2* rs13181 showed significant associations in Europeans but not in Asians under the dominant model. Nevertheless, the association analysis between polymorphisms and chemotherapy response from that study still yielded non-significant results.[20]

However, other reports presented varying results between polymorphisms in *ERCC2* and the clinical outcomes of platinum-based chemotherapy.[36,37] Based on all the data we have gathered, research on *ERCC2* rs13181 is needed to support the evidence level and to provide additional information regarding the relationship of this SNP with the response to platinum-based chemotherapy in Asian populations, as it is known that this gene is significantly influenced by race.

Materials and Methods

Study Design and Population

This study obtained ethical approval from the Research Ethics Commission of Dr. H.A. Rotinsulu Lung Hospital and Dharmais Cancer Hospital, in accordance with the requirements of the Helsinki Declaration. Additionally, informed consent was obtained from all participants prior to their involvement in the study. Additionally, informed consent was obtained from all participants prior to their involvement in the study. An observational cohort study was conducted at Dr. H.A. Rotinsulu Lung Hospital, Bandung and Dharmais Cancer Hospital, Jakarta, Indonesia which focused on inpatients with inoperable (stage III and/ IV) NSCLC treated with PB chemotherapy as first-line and exhibiting wildtype *EGFR* mutations. Data collection was focused on the analysis of genotypes using 3 mL whole blood samples, as well as the retrieval of medical records containing patient profiles, including age, gender, history of alcohol and smoking, histology type, cancer stage, and details of the chemotherapy regimen.

Smoking and alcohol history is categorized into "former" and "never" classes. A "former smoker" is defined as someone who has smoked at least 100 cigarettes in their lifetime and had quit smoking at the time of the interview. A "former alcoholic" is defined as someone who has had a history of consuming at least one drink but has not consumed any alcohol in the past year. Evaluate the effectiveness of the chemotherapy response using the Response Evaluation Criteria in Solid version 1.1 (RECIST 1.1) criteria after the completion of chemotherapy fourth cycles based on the results of Computed Tomography (CT) scans of the thorax. RECIST 1.1 results were categorized into responders including Complete Response (CR) and Partial Response (PR) as well as non-responders, namely Stable Disease (SD) and Progressive Disease (PD). However, SD was considered a responder criterion for patients at advanced cancer stages (IVA and IVB). Patients who were lost to follow-up, delayed chemotherapy for more than two cycles, changed regimen before RECIST 1.1 was obtained, had a comorbid disease treated with immunosuppressants or antiviral medications, had incomplete medical records, or untraceable RECIST 1.1 results were excluded.

Genotyping Analysis

Vacutainers without anticoagulants were used to collect 3 mL of whole blood, leading to the separation of serum and blood clot components. Subsequently, DNA was isolated from the blood clot and PCR was conducted before analyzing the polymorphisms using the Sanger sequencing method. The Forward Primer was (F): 5'-GCC CGC TCT GGA TTA TAC G - 3' while the Reverse Primer was (R): 5'-CTA TCA TCT CCT GGC CCC C-3' with an expected fragment length of 436 bp.

Statistical Analysis

The statistical data analysis was conducted in two stages, the first stage entailed the distribution of genotype frequencies and testing for Hardy-Weinberg genetic equilibrium using the chi-square test with a significance level of P=0.05. Subsequently, the association between polymorphisms and chemotherapy effectiveness was analysed using a bivariate approach to estimate the Odds Ratio and 95% Confidence Interval (CI). The presence or absence of a significant relationship between these variables was tested using the Chi-Square ($\chi 2$) method.

Results

Genotype Distribution and Frequency

The distribution of all genotypes including wild-type, heterozygous, and homozygous polymorphic variants with Hardy-Weinberg equilibrium (HWE) is presented in Table 1. This study showed that there was no significant difference between the observed frequencies and the expected frequencies. In other words, the genotype frequencies conformed to the HWE. The p-value exceeded the designated significance level (α) ($0.917 > 0.05$) and the calculated Chi-Square value was less than the critical value from the table ($0.174 < 5.991$). Consequently, the null hypothesis (H0) was accepted, and the alternative hypothesis (H1) was rejected.

Table 1 Hardy-Weinberg Equilibrium Test

ERCC2 rs13181 Genotype	Observation (*O*)	Expectation (*E*)	Proportion	Allele Freq	Hardy-Weinberg	
Wild Type Homozygote (AA)	68	67.686	0.829	0.909	p^2	0.825
Heterozygote Mutant (AC)	13	13.628	0.159		$2pq$	0.166
Homozygote Mutant (CC)	1	0.686	0.012	0.091	q^2	0.008
Variation of allele frequency	0,091					
χ^2 value	0.174					
p-value	0.917					

Note: χ^2 Chi-square test.

Characteristics of Patients

A total of 268 patients with cytologically or histologically confirmed NSCLC with wildtype profile of *EGFR*, treated with PB chemotherapy as first-line treatment, were recruited. All 268 patients provided signed informed consent prior to their participation in the study. The patients were followed up until the completion of at least four cycles of chemotherapy to obtain the RECIST 1.1 data. Finally, 82 patients met the inclusion criteria, with the majority being male (64.6%) and older than 57 years old (50%) (p=0,033). In terms of lung cancer risk factors, a significant association was found between gender and the history of smoking, with the majority of male patients being former smokers (62,2%), while only a small percentage of females had a history of smoking (7,3%) with p<0,05. However, there was no significant association with alcohol consumption habit history based on gender.

The majority of patients, regardless of gender, were at an advanced stage, either IVA or IVB, with adenocarcinoma as the predominant histological type. Treatment was carried out using PB chemotherapy combined with non-pemetrexed, namely taxane (Table 2). Furthermore, multivariate analysis showed that adenocarcinoma posed a higher risk of being categorized as non-responders compared to non-adenocarcinoma types including squamous and large cell carcinoma (OR=0.660, CI: 0.244–1.785). Similarly, patients with a history of smoking and alcohol consumption were also at higher risk of being non-responders (OR=0.684, CI: 0.234–2.004 and OR=0.829, CI: 0.299–2.299). Patients older than 57 years

Table 2 Characteristics of Patients and Clinical Features

Patients Characteristics	Number of Patients n (%) N = 82	Gender		*p-value*
		Male, n (%)	Female, n (%)	
Age				
< 57 y.o	29 (35.4)	15 (18.3)	14 (17.1)	0.033*
≥ 57 y.o	53 (64.6)	41 (50.0)	12 (14.6)	
Histopathology				
Adenocarcinoma	49 (59.8)	31 (37.8)	18 (22.0)	0.342
Non-Adenocarcinoma	33 (40.2)	25 (30.5)	8 (9.8)	
Clinical staging				
III	28 (34.1)	23 (28.0)	5 (6.1)	0.091
IV	54 (65.9)	33 (40.2)	21 (25.6)	
Smoking status				
Former	57 (69.5)	51 (62.2)	6 (7.3)	0.001*
Never	25 (30.5)	5 (6.1)	20 (24.4)	
Alcohol consumption				
Former	25 (30.5)	20 (24.4)	5 (6.1)	0.211
Never	57 (69.5)	36 (43.9)	21 (25.6)	
Chemotherapy regimen				
Platinum+Pemetrexed	33 (40.2)	20 (24.4)	13 (15.9)	0.324
Platinum+Non-Pemetrexed	49 (59.8)	36 (43.9)	13 (15.9)	

Notes: *statistically significant, chi-square test.

old have a potentially higher risk of being categorized as non-responders to PB therapy (OR=1.971, CI: 0.681–5.709). The adjusted odds ratio analysis, a method for confounding analysis, showed differences in interpretation for histopathology and smoking status (OR=1.146, CI: 0.245–5.360 and OR=1.412, CI: 0.289–6.893). However, the statistical results did not indicate any significant associations between all the patient characteristics and the treatment outcomes according to RECIST 1.1 (p > 0.05) (Table 3).

Genetic Polymorphism and RECIST 1.1

The results showed that among the Indonesian population, the majority were wildtype (AA) for *ERCC2* rs13181 (82.9%). Regardless of genetic polymorphism, 58 (70.7%) out of the 82 patients were classified as responders. Among these, patients with the wildtype genotype comprised 82.7% of the responder category. The results showed an odds ratio (OR) of 1.389 for the AC genotype, indicating that patients with this variation had 1.389 times the odds of responding to treatment compared to those with the AA variation. Additionally, polymorphisms in *ERCC2* rs13181, specifically the mutant genotype (AC+CC), tend to have a chemotherapy response categorized as a responder (OR=1.042, CI: 0.292–3.715). When adjusted for clinical staging and regimen factors, the mutant genotype had a worse chemotherapy response than the wildtype (OR= 0.970, CI: 0.263–3.568). Based on the statistical analysis results, no significant association was found with chemotherapy response (P>0,05) (Table 4).

Discussion

Lung cancer has sex-specific trends with males generally having a higher lifetime risk of development. These differences can be attributed to environmental factors, including smoking status, along with inherent biological differences, such as the contribution of sex hormones and differences in immune responses.[38,39] Approximately 80% of lung cancer cases in men are attributed to smoking. Among the various types of non-small cell lung cancer (NSCLC), squamous cell carcinoma (SCC) has a particularly strong association with smoking.[40] This study found similar results as the majority of male patients had a history of smoking (62.2%). There was also a statistically significant difference based on gender in

Table 3 Effect of *ERCC2* rs13181 on Treatment Outcomes

Variables	Number of Patients n (%) N = 82	Treatment Outcome (RECIST)			p-value		p-value
		Response n (%)	Non-response n (%)	OR (95% CI)		Adjusted OR (95% CI)	
Gender							
Male	56 (68.3)	37 (45.1)	19 (23.2)	0.464 (0.151–1.423)	0.271	0.435 (0.89–2.117)	0.303
Female	26 (31.7)	21 (25.6)	5 (6.1)	Reff.		Reff.	
Age							
< 57 y.o	29 (35.4)	23 (28.0)	6 (7.3)	1.971 (0.681–5.709)	0.313	1.938 (0.579–6.489)	0.283
≥ 57 y.o	53 (64.6)	35 (42.7)	18 (22.0)	Reff.		Reff.	
Histopathology							
Adenocarcinoma	49 (59.8)	33 (40.2)	16 (19.5)	0.660 (0.244–1.785)	0.566	1.146 (0.245–5.360)	0.863
Non-Adenocarcinoma	33 (40.2)	25 (30.5)	8 (9.8)	Reff.		Reff.	
Clinical staging							
III	28 (34.1)	16 (19.5)	12 (14.6)	0.381 (0.142–1.021)	0.091	0.454 (0.156–1.327)	0.149
IV	54 (65.9)	42 (51.2)	12 (14.6)	Reff.		Reff.	
Smoking status							
Former	57 (69.5)	39 (47.6)	18 (22.0)	0.684 (0.234–2.004)	0.667	1.412 (0.289–6.893)	0.670
Never	25 (30.5)	19 (23.2)	6 (7.3)	Reff.		Reff.	
Alcohol consumption							
Former	25 (30.5)	17 (20.7)	8 (9.8)	0.829 (0.299–2.299)	0.923	0.854 (0.272–2.677)	0.791
Never	57 (69.5)	41 (50.0)	16 (19.5)	Reff.		Reff.	
Chemotherapy regimen							
Platinum+Pemetrexed	33 (40.2)	20 (24.4)	13 (15.9)	0.445 (0.169–1.173)	0.160	0.313 (0.070–1.402)	0.129
Platinum+Non-Pemetrexed	49 (59.8)	38 (46.3)	11 (13.4)	Reff.		Reff.	

Notes: Adjusted OR (gender, age, histopathology, cancer stage, smoking status, alcohol consumption, and regimen).

Table 4 Association Between *ERCC2* rs13181 with Platinum-Based Chemotherapy Responses Based on RECIST 1.1

Polymorphism	Number of Patients n (%) N = 82	Treatment Outcome (RECIST)			*p*		*p*
		Response n (%)	Non-response n (%)	OR (95% CI)		Adjusted OR (95% CI)	
ERCC2 rs13181							
AA	68 (82.9)	48 (58.5)	20 (24.4)	Reff.	0.644	Reff.	
AC	13 (15.9)	10 (12.2)	3 (3.7)	1.389 (0.345–5.585)	–	1.274 (0.308–5.266)	0.738
CC	1 (1.2)	0 (0.0)	1 (1.2)	–	0.950	–	
AC+CC	14 (17.1)	10 (12.2)	4 (4.9)	1.042 (0.292–3.715)		0.970 (0.263–3.568)	0.963
AA	68 (82.9)	48 (58.5)	20 (24.4)	Reff.		Reff.	

Notes: Adjusted OR (clinical staging and regimen).

relation to smoking history (p=0.000). A large proportion of male patients had either quit smoking upon being diagnosed with lung cancer or stopped during the chemotherapy treatment after one or two cycles. Although only a few patients had a history of alcohol consumption (30,5%), both smoking and alcohol consumption are well-established risk factors for lung cancer. Smoking is directly associated with lung cancer mortality, causing premature deaths. It contributes to approximately 30% of total cancer deaths, and about 90% of lung cancer deaths.[41,42]

The reduced effectiveness and tolerance of chemotherapy due to alcohol consumption are associated with the activation of cell growth cycles and the stimulation of survival pathways that manifest as apoptosis resistance.[43–45] Alcohol consumption also influences the prognosis and survival rate of cancer patients. Statistical data from 2002, for instance, indicated that 3.5% of cancer deaths were connected with alcohol.[46] This may explain the odds ratio (OR) of smoking and alcohol consumption history in relation to treatment outcomes, posing a risk for non-responder categorization among patients, although the result was not statistically significant. Similarly, regarding age, the majority of males above 57 years had a statistically significant difference compared to females (p=0.033). Previous studies on NSCLC in the US indicated that new cases/incidence, and the prevalence of lung cancer, are predominantly found in the elderly. Patients with stage IV NSCLC aged 65 years or older were most likely to be untreated (38.3%).[47]

The choice of chemotherapy regimen may also influence treatment outcomes. For instance, adenocarcinoma patients may benefit from pemetrexed. Although cisplatin is slightly more effective as a platinum agent, it has been associated with various side effects. Evidence suggests that patients with a performance status (PS) of 2 may require only one drug, typically not platinum-based.[48–50]

The underlying theory regarding the association of rs13181 polymorphisms with chemotherapy response is the drug resistance mechanism, which entails DNA repair activity that could inhibit the apoptosis process of cancer cells. The polymorphism in rs13181, which codes for a protein component of the DNA helicase enzyme associated with the recognition of damaged DNA sites caused by platinum agent, and unwinding process leads to alterations in the amino acid Lysine (Lys) to Glutamine (Gln). This alteration manifests as changes in Nucleotide Excision Repair (NER) activity, leading to a decrease in the effectiveness of PB chemotherapy. It primarily impacts the incision stage of the NER mechanism, causing direct changes in NER activity.[21,51–53] From the previous meta-analysis study, *ERCC1* rs11615 and *ERCC2* rs13181 were found to be the best predictors of chemotherapy response (Overall Survival and/ Progression Free Survival) among many other genes associated with the chemotherapy resistance mechanism. Several other polymorphisms include *ERCC1* rs3212986 (ORR), *XPA* rs1800975 (ORR), *ERCC2* rs1052555 (OS, PFS), *XPG* rs2296147 (OS), *XRCC1* rs1799782 (ORR), *XRCC3* rs861539 (ORR), *GSTP1* rs1695 (ORR), *MTHFR* rs1801133 (ORR), and *MDR1* rs1045642 (ORR).[30]

Among the nine genes associated with chemotherapy response or clinical outcomes, the majority were associated with DNA repair mechanisms including *EXCC1*, *XPA*, *XPD*, *XPG*, *XRCC1*, and *XRCC3*. Genes related to chemotherapy resistance through drug pharmacokinetics mechanisms include drug influx and efflux (*MDR1*) as well as metabolism and detoxification (*GSTP1*), while the last gene, *MTHFR*, plays a role in the DNA synthesis process.[19] Another meta-analysis study stated that *ERCC2* rs13181, along with other Single Nucleotide Polymorphism (SNPs) such as *ERCC1* (rs11615)

and *XRCC1* (rs25487, 1,799,782), ranked among the top three predictor genes for sensitivity/response to PB chemotherapy. These genes are associated with DNA repair pathways, both in NER and Base Excision Repair (BER).[18]

Previous studies have yielded positive statistically significant results regarding the association between rs13181 and the impact on the clinical outcomes of PB chemotherapy. For example, a study of 72 subjects from the US population found that individuals with the A allele were significantly less likely to respond to treatment (HR 0.33; 95% CI 0.13–0.83).[54] Similarly, a case-control study involving 1,016 subjects from the Chinese population found that the mutant (C) allele significantly increased the chemotherapy response (OR 2.37; 95% CI 1.12–5.01; p=0.021).[55] Furthermore, the results of a meta-analysis with 2,125 subjects, including both Asian populations (China and Korea) and European populations (Spain, Italy, UK, Netherlands), showed significant results for the overall response rate (OR 0.81; 95% CI 0.66–0.99)[18.] In contrast, another meta-analysis with 29,478 subjects showed no significant results for the response rate across five comparison models (allele comparison, homozygote comparison, heterozygote comparison, recessive model, and dominant model).[20]

Based on the results of this study indicated no significant association between the mutant polymorphism (AC+CC) and therapeutic response (p=0.950) despite an odds ratio (OR) value of 1.042 (95% CI: 0.292–3.715) found in the analysis. Further analysis was performed by adjusting the OR for variables such as cancer stage and regimen. However, the results showed no significant association (aOR: 0.970; 95% CI: 0.263–3.568; p=0.963). These findings are in line with the majority of reports on *ERCC2* rs13181 in PhamGKB. Differences from other studies discussed earlier may be attributed to study design and sample size contributing to research outcome variations. Additionally, in previous studies, the response was assessed in the second cycle,[54] whereas in Indonesia, the evaluation is performed in the fourth cycle, following the national healthcare coverage policies.

Another potential factor influencing the study results is genotype distribution. A study in a Japanese population reported genotype distribution results where the AA genotype was dominant, with 73 subjects (98.6%), the AC genotype with one subject (1.4%), and no subjects with the CC genotype. The high dominance of the AA genotype complicates the interpretation of the relationship between allelic variation and response.[54] In addition, based on meta-analysis, population stratification contributes to high heterogeneity scores in an analysis.[20] In this study, the results of genotype identification showed that the AA genotype dominated, with 68 subjects (82.9%), followed by the AC genotype with 13 subjects (15.9%), and the CC genotype with one subject (1.2%). A study reported that genetic variation in the Indonesian population is diverse due to the interaction of multiple ancestral populations. This variation reflects a unique genetic composition within the population, which may lead to differences in treatment response compared to European and other Asian populations.[35]

During advanced stages, particularly in the metastasis of lung cancer, the interpretations of RECIST 1.1 results may vary. For instance, the classification of stable disease as a responder has been a subject of debate. Previous studies suggested that in advanced NSCLC patients given a combination of chemotherapy and targeted therapy as initial treatment followed by assessment using RECIST 1.1 criteria, stable disease (SD) demonstrated a comparable overall survival advantage to partial response (PR). This implies that assessing the effectiveness of anti-tumor treatments based solely on RECIST criteria may not always be consistent with overall survival benefits. Consequently, a more comprehensive assessment approach is needed to enhance the precision of RECIST 1.1 criteria, particularly for patients taking chemotherapy combined with targeted therapy for NSCLC.[56,57]

As previously mentioned, the limited amount of data can influence the confidence interval and probability values, underscoring the need for further studies with a more adequate sample size. However, the results may be considered in the evaluation of chemotherapy response especially for patients treated using PB chemotherapy for NSCLC in Indonesia. To obtain clinical confirmation regarding the association between rs13181 and the clinical outcomes of PB chemotherapy, further cohort studies with larger sample sizes, including subjects representing clusters from different regions of Indonesia, and more comprehensive sample data to minimize bias are required. Additionally, several single nucleotide polymorphisms (SNPs) should be analysed in association with resistance mechanisms in PB treatment, including pharmacodynamic and pharmacokinetic.

Conclusion

In conclusion, there were no statistically significant associations between *ERCC2* rs13181 polymorphisms and chemotherapy response according to RECIST 1.1 criteria. However, this research highlights the presence of genetic variation within the Indonesian population, with the AA genotype being the most prevalent, which may influence chemotherapy responses. These findings offer preliminary data and lay the foundation for future, more extensive cohort observational studies aimed at more accurately assessing potential clinical implications.

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Disclosure

The authors report no conflicts of interest in this work.

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