Original Article

The Significance of SLC29A1 Gene Polymorphisms in Response to Gemcitabine-Based Chemotherapy in Metastatic NSCLC

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Abstract

Background: *z* accounts for 80%–85% of lung cancer, and gemcitabine is essential for treatment. SLC29A1, a transmembrane protein, binds to gemcitabine. Single-nucleotide polymorphisms (SNPs) in SLC29A1 genes may affect its pharmacokinetics. **Objectives:** To evaluate the impact of SLC29A1 gene polymorphism on gemcitabine response in patients with non-small-cell lung cancer (NSCLC). **Materials and Methods:** This is a cross-sectional study comprising 98 NSCLC patients aged 30–70 under gemcitabine-based chemotherapy. Demographic and clinical characteristics of the patients were collected. The response is assessed by evaluation criteria in solid tumors, and then, patients are classified as responders or non-responders. Chemotherapy side effects were assessed. Gene fragment corresponding to SLC29A1 rs760370 gene polymorphism was amplified using four primers. The genotyping was performed through amplification refractory mutation system polymerase chain reaction. **Results:** This study revealed that responsive patients had a mean tumor size of 34.6 ± 30.94 cm^2, significantly lower than non-responsive patients. After four to six treatment cycles, responsive patients had a mean tumor size reduction of 11.82 ± 13.98 cm^2, while non-responsive patients had a reduction of 15.31 ± 6.27 cm^2. Females have more tumor size reduction. The most common side effects are vomiting, anemia, leukopenia, neutropenia, and nausea. The frequency of mutant homozygous genotype (GG) of SLC29A1 rs760370 was higher in non-responsive vs. responsive patients (14.58% vs. 8%) compared with the AA and AG genotypes and suggests that genes affect chemotherapy effectiveness, predicting its presence affects therapeutic plans of patients. **Conclusion:** Genetics impacts chemotherapy effectiveness, with SNPs in genes potentially affecting treatment plans and predicting disease outcomes.

Keywords: Gemcitabine, non-small-cell lung cancer, single-nucleotide polymorphism, SLC29A1

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of lung cancer cases. It is linked to smoking, genetics, and environmental factors. Early diagnosis and screening are essential for efficient treatment planning.[1] NSCLC does not affect all smokers. Lung cancer can occur without smoking if there are certain risk factors or environmental exposures.[2] Patients present with signs and symptoms such as shortness of breath, cough, and shoulder pain.[3] Lung cancer stages are classified using the IASLC seventh tumour-nodes-metastasis (TNM) staging system for effective treatment.[4] TNM system analyzes tumor burden using chest X-rays, computed tomography (CT) scans, positron emission tomography scans, and biopsy, resulting in staging systems (I–IV).[5] Lung cancer treatment advances with genetics, molecular medicine, and targeted therapies.[6] Targeted therapy is crucial for advanced lung cancer patients; adjuvant chemotherapy is crucial for stage II–III NSCLC and early-stage patients.[7] Chemotherapy is the gold standard for advanced NSCLC, but resistance poses challenges, requiring combination with surgery.[8]

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Gemcitabine is a chemotherapeutic agent that has shown potential in treating various human cancers. It can be used as a single- or second-line treatment for pancreas, lung, breast, colon, and ovary cancers and others.[9,10] Genetic variations altering membrane transporters, activating and deactivating enzymes, and pharmacological targets like ribonucleotide reductase affect cancer cell therapy efficiency.[11] To evaluate cancer therapy, tumor burden changes must be measured. Objective response and progression-free survival (PFS) are important goals. For clinical trials, the response is assessed by evaluation criteria in solid tumors (RECIST) guideline simplifies and standardizes tumor response evaluation.[12] The aim of the study was to assess gemcitabine response in NSCLC patients and examine how single-nucleotide polymorphisms (SNPs) in SLC29A1 gene affect gemcitabine treatment and its side effects.

Materials and Methods

This is a cross-sectional study which includes a total of 98 patients with NSCLC completed four to six cycles of treatment with gemcitabine chemotherapy at the Oncology Department, Baghdad Medical City, Oncology Teaching Hospital, Oncology Department at Al Imamain Al Kadhumain Medical City, and Al Amal Hospital. Patients with advanced NSCLC stages under palliative therapy were excluded from the study. The laboratory work was performed at the medical research unit, College of Medicine, Al-Nahrain University.

Data collection

The following data were collected from patients' records: demographic data, including age, gender, smoking status, comorbidities, family history of malignancy, and occupation; clinical data, including treatment protocol; and tumor characteristics, including tumors size, site, primary tumor classification, lymph node involvement, and tumor grade and stage.

Patients' categorization

Patients were categorized into responsive and non-responsive, and their responses were evaluated using RECIST guidelines, which classify response into complete response, partial response, progressive disease, and stable disease according to tumor size. Tumor response was assessed through clinical evaluation and CT scans every two treatment cycles. Furthermore, patients were assessed for the efficacy and toxicity of treatment, and the side effects of chemotherapy were reported.

Blood samples, genomic DNA extraction, and gene amplification

About 3 mL of venous blood was drawn from each participant and collected in ethylene diamine tetra-acetic acid tubes. A ready commercial kit (Genaid, Taiwan) was used for genomic DNA extraction. The company's protocol was applied precisely.

Table 1: Primers used for amplification and genotyping of SLC29A1 rs760370 using ARMS-PCR

Primers	Sequence 3′–5′
Outer primers	F-5′-GGGACACTCAGTAGAGGGAGGGCAAAAG-3′
	R-5′-AGGCTACCTCAGAATGGCTGTACCCCAG-3′
Inner primers	F-5′-CTTGGGTGGAGGTGGAGACAGGTTTACA-3′
	R-5′-TATGGTGGGGTTGTCTTTCACTCCTTTCG-3′

Four primers were used in gene amplification and genotyping of SLC29A1 rs760370 using amplification refractory mutation system (ARMS), as shown in Table 1. Primers were imported from Bioneer Company, Korea in lyophilized form. To make a stock solution with a final concentration of 100 pmol/L, lyophilized primers were dissolved in DNase/RNase-free water. After that, a working solution with a concentration of 10 pmol/L was made by mixing 10 µL of the stock solution with 90 µL of distilled water. Four µL of template DNA and 2 µL of primers were added to each master mix tube.

The following polymerase chain reaction (PCR) conditions were applied: initial denaturation 95°C for 5 min, denaturation 94°C for 30 s, annealing for 30 s, elongation 72°C for 1 min, and final elongation 72°C for 7 min. The PCR products were subjected to 2% gel electrophoresis, after which ultraviolet light was used to visualize the banding pattern.

Statistical analysis

SPSS software version 25.0 was used to conduct statistical analysis (SPSS, Chicago, Illinois, USA). The mean and standard deviation of continuous data were calculated and analyzed using the Student *t*-test. The genotype deviation from Hardy–Weinberg equilibrium (HWE), which assumes that the genetic variation in a population will remain constant from one generation to the next in the absence of disturbing factors such as selection and migration, was calculated using chi-square, which was also used to assess binomial variables given as numbers and percentages. To investigate the link between the SLC29A1 gene polymorphism and responsiveness to gemcitabine, binary logistic regression was used to calculate the odds ratio and the related 95% confidence intervals (CIs). A P value less than 0.05 was considered to indicate a statistically significant difference.

Ethical approval

The research was conducted in accordance with the Helsinki Declaration's ethical criteria. Before taking the sample, the patients' verbal consent was obtained. The

study protocol and the subject information and consent form were reviewed and approved by the Institute Review Board, College of Medicine, Al-Nahrain University according to the document number (Ref.: IBR/101 on February 27, 2024).

Results

Demographic characteristics of the patients

The study included a total of 98 patients with pulmonary squamous cell carcinoma treated. The mean age of responsive and non-responsive patients was 56.04 ± 10.12 years and 57.79 ± 9.02 years, respectively, with no significant difference. Males and females were evenly distributed in both groups with no significant difference. Likewise, the two groups were comparable regarding weight, height, and body mass index (BMI) with no significant differences. Smoking was common in both groups and reported in 72% and 77.07% of responsive and non-responsive patients, respectively, with no significant difference. About two-thirds of patients in each group had Eastern Cooperative Oncology Group (ECOG) score 2 with no significant differences [Table 2].

Therapeutic and clinical characteristics of the patients

Hypertension and ischemic heart disease (IHD) were slightly more frequent among non-responsive patients (37.5% and 14.58%, respectively) than responsive patients (24% and 10%, respectively); however, the differences were not significant. In contrast, other comorbidities were non-significantly more frequent among responsive than non-responsive patients (8% vs. 6.35%). The initial tumor size in the responsive group was 45.15 ± 36.67 cm^2 which was comparable to that of non-responsive patients (42.26 ± 33.18 cm^2) with no significant difference. However, after four to six cycles of treatment, the mean final tumor size in responsive patients became 34.6 ± 30.94 cm^2 which was much lower than that of non-responsive patients (57.86 ± 43.8 cm^2) with a highly significant difference. About three-fourths of the patients in either group received six treatment cycles with no significant difference between the two groups [Table 3].

Reduction in tumor size

The reduction in tumor size (based on CT scan examination) in the responsive group was 11.82 ± 13.98 cm^2 (range: 2.27–57.51 cm^2) compared with −15.31 ± 6.27 cm^2 (range: −2.7 to −24.18 cm^2) in the non-responsive group. Kruskal–Wallis test revealed a highly significant difference in the reduction in tumor size between the two groups [Figure 1].

Adverse effects of treatment

A total of 11 adverse effects were reported in responsive and non-responsive patients. Generally, there were no significant differences in the occurrence of adverse effects between responsive and non-responsive patients. The most common adverse effects were vomiting (86% and 77.08%), anemia (84% and 81.25%), leukopenia (38% and 35.42%), neutropenia (36% and 41.67%), and nausea (32% and 43.75%) in responsive and non-responsive patients, respectively [Table 4].

Table 2: Demographic characteristics of the patients

Variables	Responsive (n = 50)	Non-responsive (n = 48)	P value
Age, years			0.369
Mean ± SD	56.04 ± 10.12	57.79 ± 9.02	
Range	38–70	34–70	
Gender			0.837
Male	25 (50%)	25 (52.08%)	
Female	25 (50%)	23 (47.92%)	
Weight, kg			0.476
Mean ± SD	66.34 ± 6.49	65.35 ± 7.13	
Range	54–83	54–82	
Height, cm			0.584
Mean ± SD	162.2 ± 6.03	162.83 ± 5.34	
Range	150–175	152–180	
BMI, kg/m^2			0.11
Mean ± SD	25.17 ± 1.44	24.61 ± 1.98	
Range	21.45–28.65	20.09–29.38	
Smoking			0.718
Never	14 (28%)	11 (22.92%)	
Ex/current smokers	36 (72%)	37 (77.07%)	
ECOG			0.16
One	9 (18%)	4 (8.33%)	
Two	33 (66%)	30 (62.5%)	
Three	8 (16%)	14 (29.17%)	

ECOG: Eastern Cooperative Oncology Group. It describes a patient's level of functioning in terms of their ability to care for themselves

Table 3: Clinical characteristics of the patients

Variables	Responsive (n = 50)	Non-responsive (n = 48)	P value
Comorbidities			
No comorbidity	12 (24%)	10 (20.83%)	0.821
Diabetes mellitus	12 (24%)	18 (37.5%)	0.147
Hypertension	15 (30%)	15 (31.25%)	0.893
Ischemic heart disease	5 (10%)	7 (14.58%)	0.489
Others	4 (8%)	3 (6.35%)	0.737
Initial tumor size, cm^2			0.151
Mean ± SD	45.15 ± 36.67	42.26 ± 33.18	
Range	3.48–120.96	14.94–127.6	
Final tumor size, cm^2			0.003*
Mean ± SD	34.6 ± 30.94	57.86 ± 43.8	
Range	0.5–101.92	16.4–142.74	
Treatment cycles			0.39
4	13 (26.67%)	9 (13.33%)	
6	37 (73.33%)	39 (86.67%)	

*Significant at $P < 0.001$

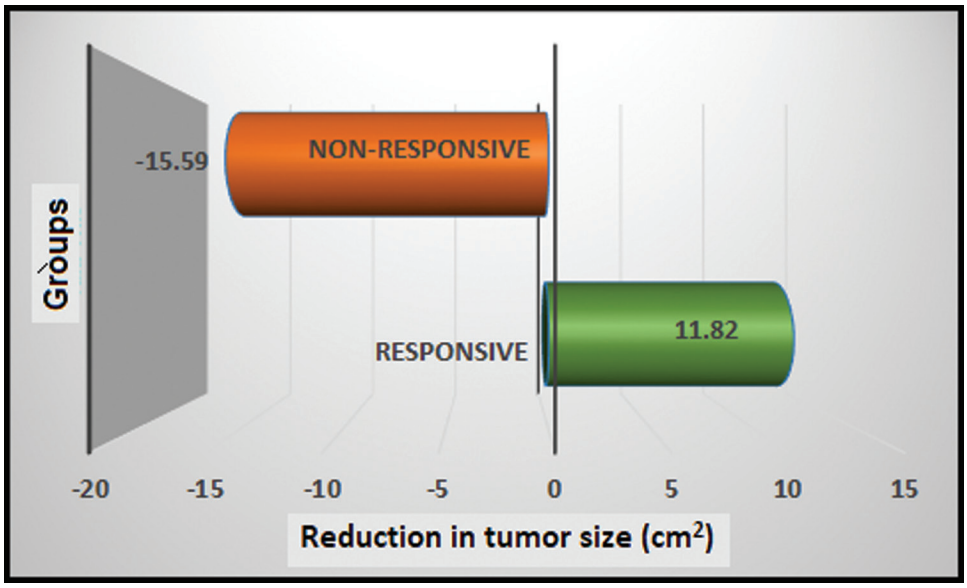

Figure 1: Reduction in tumor sizes in responsive and non-responsive patients

Table 4: Adverse effects of treatment in responsive and non-responsive patients

Effects	Responsive (n = 50)	Non-responsive (n = 48)	P value
Leukopenia	19 (38%)	17 (35.42%)	0.791
Neutropenia	18 (36%)	20 (41.67%)	0.565
Nausea	16 (32%)	21 (43.75%)	0.230
Vomiting	43 (86%)	37 (77.08%)	0.624
Alopecia	3 (6%)	2 (4.17)	1.00
Anemia	42 (84%)	39 (81.25%)	0719
Hematuria	7 (14%)	4 (8.33%)	03.74
Thrombocytopenia	2 (4%)	0 (0%)	0.495
Pain	3 (6%)	3 (6.25%)	1.00
Fatigue	7 (14%)	9 (18.75%)	0.525
Constipation	11 (22%)	10 (20.83%)	0.918

Molecular assays

SNP in two genes (SLC29A1 rs760370 and CMPK1 rs1044457) were investigated for their association with the response to gemcitabine-based chemotherapy in patients with metastatic NSCLC.

SLC29A1 rs760370

Primers were used to amplify and genotype the SLC29A1 rs760370 polymorphism using ARMS technique. The result of gel electrophoresis is shown in Figure 2. This SNP had three genotypes in responsive and non-responsive patients: These were AA, GA, and GG. The distribution of these genotypes was in good accordance with HWE.

The frequency of the different genotypes in responsive and non-responsive patients is comparable, with no significant difference. Although the mutant homozygous genotype (GG) was more frequent among non-responsive patients than responsive patients (14.58% vs. 8%), the difference was not significant. Similarly, there was no significant difference in the different models or allele distribution between the two groups [Table 5].

Discussion

Gemcitabine, a nucleoside analog, has shown promising results in managing metastatic NSCLC and other malignancies. It inhibits DNA synthesis, causing cell cycle cessation and apoptosis. Gene polymorphisms may affect its efficacy and adverse reactions.[11] Detecting genetic variations is crucial for managing chemotherapy, as they impact an individual's reaction to pharmacotherapy. Polymorphisms in genetic sequences encode metabolic enzymes and targets, affecting a significant proportion of chemotherapy medications. Identifying these polymorphisms can predict treatment response and improve therapeutic results.[13]

In a 2006 Phase III clinical trial, Sandler *et al*. found that gemcitabine and carboplatin combined significantly improved overall survival and PFS in metastatic NSCLC patients. The combination therapy showed a response rate nearly three times higher than carboplatin alone, and the median survival time was significantly longer in the group receiving the combination therapy. This highlights the efficacy of gemcitabine in improving overall survival and PFS in metastatic NSCLC patients.[14] Schiller *et al*. found gemcitabine combination significantly improves therapeutic outcomes compared with cisplatin alone, highlighting its effectiveness in enhancing response rates.[15]

The response rate to chemotherapy medications is influenced by factors like targeted treatments and

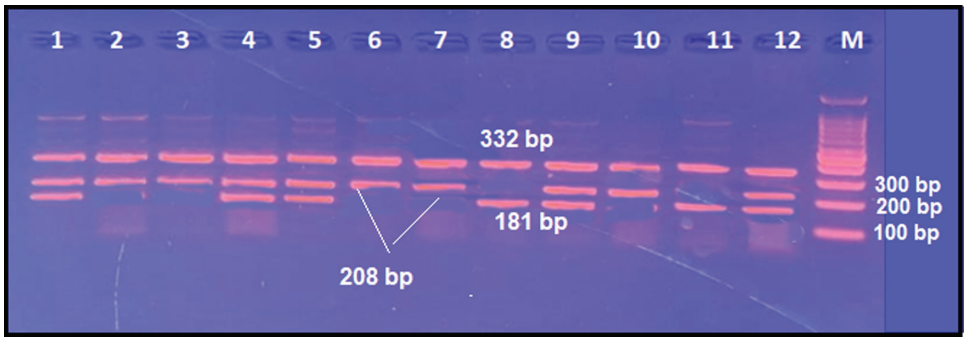

Figure 2: Gel electrophoresis of rs760370 gene polymorphism amplified with amplification refractory mutation system method. The PCR product was stained with ethidium bromide. Lanes 1, 4, 5, 9, and 12: AG genotype; lanes 2, 3, 6, 7, and 10: AA genotypes; lanes 8 and 11: GG genotype. M: 100 bp DNA ladder

Table 5: The frequency of different genotypes and alleles of the polymorphism rs760370 in patients and controls

rs760370	Responsive	Non-responsive	*P* value	OR (95% CI)
	−50	−48		
Genotypes				
AA	27 (54%)	24 (50%)	0.595	1
AG	19 (38%)	17 (35.42%)	0.988	1.01 (0.43–2.36)
GG	4 (8%)	7 (14.58%)	0.324	1.97 (0.51–7.56)
HWE	0.798	0.188		
Dominant model				
AA + GA	46 (92%)	41 (85.42%)	0.309	1
GG	4 (8%)	7 (14.58%)	0.18	1.96 (0.54–7.19)
Recessive model				
AA	27 (54%)	24 (50%)		1
GA + GG	23 (46%)	24 (50%)		0.55 (0.23–1.32)
Alleles			0.692	
A	73 (73%)	65 (67.71%)		1
G	27 (27%)	31 (32.29%)		1.17 (0.53–2.6)

immunotherapy advancements. Gemcitabine-based treatment's efficacy is influenced by these factors, as personalized immunotherapy allows for tailored management strategies through biological and immunogenic testing.[16]

This study observed a relatively homogeneous gender as well as age distribution among both the responsive and unresponsive groups. Additionally, no statistically significant variations are found between the two groups in terms of BMI, smoking history, and ECOG2 (tumor performance status). The prevalence of hypertension and IHD is marginally higher among non-responsive patients (37.5% and 14.58%, respectively) compared with responsive patients (24% and 10%, respectively). However, these differences did not reach statistical significance.

A negative correlation exists between cancer patients' chronological age and their response to gemcitabine therapy, specifically in terms of tumor size reduction. This is due to the fact that more than 40% of lung cancer diagnoses are made in individuals aged 70 and above. The geriatric population has a higher prevalence of health conditions and is less able to tolerate aggressive medical interventions, especially chemotherapy. Elderly individuals are also more likely to have concurrent medical conditions, such as cardiovascular disorders, compared with younger patients. This could explain the disparity in response rates to gemcitabine between younger and older patients, with a homogeneous distribution of age across both responsive and unresponsive groups.[17]

However, responding patients show a significant positive connection between tumor size reduction and treatment cycles ($r = 0.305$, $P = 0.031$). Four to six gemcitabine cycles are suggested for NSCLC treatment. Treatment duration increases responsiveness. Because quiescent cancer cells are always present. Chemotherapy targets mitosis-undergoing cells. Resting cells are invulnerable. Each cycle kills more tumor cells. Hypertension disrupts the delicate balance between pro- and anti-angiogenic factors, promoting tumor growth. It can also alter the tumor's response to gemcitabine.[18,19] Oxidation and inflammation caused by uncontrolled blood pressure enhance malignant cell growth and reduce therapy efficacy.[20,21]

Comorbidities are slightly more common in patients who responded to treatment (8% vs. 6.35%), but this difference is not statistically significant. The responsive group's initial tumor size was $45.15 \pm 36.67\,cm^2$, whereas the non-responsive group's initial tumor size was $42.26 \pm 33.18\,cm^2$. There is no statistically significant difference between the two groups. After four to six treatment cycles, positive responders have an average tumor size of $34.6 \pm 30.94\,cm^2$, compared to $57.86 \pm 43.8\,cm^2$ for unresponsive patients. Both

groups differ statistically. Both groups have 75% of patients complete six treatment cycles, with no statistical difference. These findings show that both groups have similar rates of comorbidities, except for genetic variation influencing treatment response. Multiple genes encode proteins that control metabolism and the cellular reuptake of gemcitabine. The researchers chose the SLC29A1 gene's SNP rs760370, which encodes a drug-uptake protein. Thus, changes in the parent gene may affect protein function. These changes help predict gemcitabine plasma concentrations.[22]

Genotype research shows that both responsive and unresponsive groups have three polymorphisms: AA, GA, and GG. Both groups' genotype distributions follow HWE principle. Receptive and non-responsive patients have similar genetic frequencies. The mutant homozygous genotype (GG) is more common in non-responsive individuals (14.58% vs. 8%), but the difference is not significant. Both groups have similar genotype and allele distributions.

Numerous studies have suggested ways that this mutation could affect gemcitabine efficacy. The variant genotype alters hENT1 expression, affecting gemcitabine uptake into malignant cells. Polymorphism may also affect hENT1 protein stability or gemcitabine binding affinity, which can affect therapeutic response.[23-25]

Hematological adverse effects affect most gemcitabine patients. Thus, reducing this toxicity would improve patient outcomes and quality of life. Juan Li *et al*. examined 13 DNA damage and folate pathway-related polymorphisms in transporters, metabolizing enzymes, targets, and genes in 132 gemcitabine-treated patients. The goal is to determine whether these genetic variations affect hematological toxicity. hENT1 rs760370, hCNT3 rs7867504, and rs4877831 were associated with severe leukopenia in the single-locus analysis.[26]

Our research found no statistically significant genetic difference between treatment responders and non-responders. Unlike the AA and AG genotypes, the mutant homozygous genotype (GG) is more common in non-responders (14.58% vs. 8%). Polymorphisms and NSCLC have been studied infrequently. Cho *et al*. studied polymorphisms in gemcitabine-treated breast cancer. The study found that those with the GG genotype for the rs760370 polymorphism in SLC29A1 had a median PFS duration of 5.6 months, while those with AA and AG genotypes had 10.4 months ($P = 0.002$ for the recessive inherited model, hazard ratio: 5.535, 95% CI: 1.839–16.656), supporting our research findings.[27]

In a separate study by Alvarellos *et al*., pancreatic cancer patients with the GG genotype in the SNPs of SLC29A1 had a poorer tumor response to gemcitabine and radiation therapy or platinum than those with the AA and AG genotypes.[28]

The above research suggests that genetic variations can help tailor chemotherapy to patients' genetics. SLC29A1 rs760370 genotype polymorphisms may predict gemcitabine response and side effects in NSCLC patients, but there is no published research.

Gusella *et al*. found that carriers with a G allele in the −706G>C SNP, which increases SLC29A1 transferring ability, have lower plasma gemcitabine clearance than carriers with the CC genotype.[29]

SLC29A1 has prognostic relevance for a subpopulation of pancreatic ductal adenocarcinoma patients who receive adjuvant gemcitabine. Gemcitabine-based chemotherapy in patients with SLC29A1 gene SNP rs760370 has a slower progression rate. These SNPs have not been linked to patient survival. However, they are promising prognostic indicators for systemic treatment efficacy and side effects.[30]

The limitations of this study are the association between SN genetic polymorphism and drug adverse effects, as this may hinder patient compliance. Further investigation is needed to understand the molecular underpinnings of additional SNPs influencing gemcitabine pharmacokinetics, and a larger sample size is needed to minimize errors. Additionally, all patients should undergo an equal six cycles of treatment for more homogeneous results.

Conclusion

Identifying genetic polymorphisms is crucial for managing chemotherapy, as they impact treatment response and improve therapeutic outcomes. These polymorphisms can be found in genes encoding enzymes, thus affecting disease outcomes.

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Conflicts of interest

There are no conflicts of interest.

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