Research Article

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Impact of cisplatin on Kasumi-1 leukemia cell line: gene expression and DNA damage

Sisplatinin Kasumi-1 lösemi hücre hattı üzerindeki etkisi: gen ekspresyonu ve DNA hasarı

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Abstract

Purpose: Leukemia is a type of cancer caused by the uncontrolled proliferation of blood cells. The purpose of this study was to investigate the effects of cisplatin (CIS), a chemotherapeutic agent used in the treatment of leukemia, on the Kasumi-1 leukemia cell line.

Materials and methods: The study measured the effect of CIS on Kasumi-1 cells by calculating IC50 values for cell viability. The mRNA expression levels of apoptosis and cell cycle-related genes were then assessed using Real-Time PCR. In addition, the effects of CIS on DNA damage were investigated using the comet assay.

Results: Significant changes in apoptosis and cell cycle-related genes were observed in CIS-treated groups. These included alterations in the mRNA levels of p53, BCL-2, CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G, and ATM genes. Comet analysis confirmed CIS's effects on DNA damage.

Conclusion: This study aimed to better understand how CIS affects genetic mechanisms in leukemia cells and provide new insights into leukemia treatment. The findings will help us better understand the role of CIS in leukemia treatment and will serve as a valuable reference for future research.

Keywords: Leukemia, acute myeloid leukemia, cisplatin, Kasumi-1 cell, DNA damage.

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Öz

Amaç: Lösemi, kan hücrelerinin kontrolsüz çoğalması sonucu ortaya çıkan bir kanser türüdür. Bu çalışmanın amacı, lösemi tedavisinde kullanılan kemoterapötik bir ajan olan sisplatinin (CIS) Kasumi-1 lösemi hücre hattı üzerindeki etkilerini araştırmaktır.

Gereç ve yöntem: Çalışmada, hücre canlılığı için IC50 değerleri hesaplanarak CIS'in Kasumi-1 hücreleri üzerindeki etkisi ölçülmüştür. Apoptoz ve hücre döngüsü ile ilgili genlerin mRNA ekspresyon seviyeleri daha sonra Real-Time PCR kullanılarak değerlendirilmiştir. Ayrıca, CIS'in DNA hasarı üzerindeki etkileri comet testi kullanılarak araştırılmıştır.

Bulgular: CIS ile tedavi edilen gruplarda apoptoz ve hücre döngüsü ile ilgili genlerde önemli değişiklikler gözlendi. Bunlar arasında p53, BCL-2, CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G ve ATM genlerinin mRNA seviyelerindeki değişiklikler yer aldı. Comet analizi CIS'in DNA hasarı üzerindeki etkilerini doğrulamıştır.

Sonuç: Bu çalışma, CIS'in lösemi hücrelerindeki genetik mekanizmaları nasıl etkilediğini daha iyi anlamayı ve lösemi tedavisine yeni bakış açıları sağlamayı amaçlamıştır. Bulgular, CIS'in lösemi tedavisindeki rolünü daha iyi anlamamıza yardımcı olacak ve gelecekteki araştırmalar için değerli bir referans görevi görecektir.

Anahtar kelimeler: Lösemi, akut miyeloid lösemi, sisplatin, Kasumi-1 hücresi, DNA hasarı.

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Introduction

Leukemia, also known as blood cancer, is a serious type of cancer that affects millions of people worldwide [1]. The detection of leukemia cancer has been linked to the uncontrolled proliferation of cancer stem cells. These cancer stem cells were first discovered in acute myeloid leukemia (AML) [2]. AML is a type of leukemia distinguished by an interruption or increase in the maturation of myeloid cells in the bone marrow. This can cause granulocytopenia, anemia, and hematopoietic failure with or without leukocytosis [3]. Chemotherapy is one of the most common treatment options for leukemia, as it is for many other cancers [4]. Chemotherapy's primary goal is to prevent cancer cells from spreading uncontrollably or to kill them. However, because this treatment method involves the use of numerous chemotherapeutic drugs, it affects both cancerous and normal healthy cells that proliferate [5]. Cisplatin is one of the most commonly used chemotherapy drugs.

CIS is an inorganic compound that belongs to the group of platinum-based chemotherapeutic drugs (Figure 1). This drug is a coordinate compound that has been widely used since 1960, when it was first developed by a group of Rosenberg University researchers [6]. In 1969, the same researchers investigated CIS's antitumor activity in leukemia and sarcoma cell lines. Furthermore, CIS is currently used as an antitumor drug in a variety of cancers, including head and neck, breast, testicular, colorectal, and bladder cancers [7].

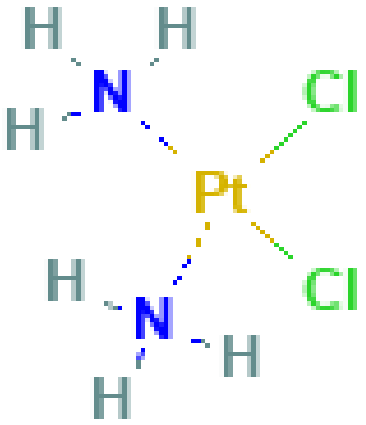

Figure 1. Chemical Structure of Cisplatin [Pubchem]

CIS is one of the most potent chemotherapeutic drug groups. However, as with other chemotherapy drugs, it has been shown to have serious side effects on healthy cells. CIS primarily damages DNA in the cells in which it first acts. It exerts its effect by passing through purine bases in DNA and forming cross-linked covalent bonds [8]. In addition to DNA damage, it inhibits RNA and protein synthesis. This causes disruptions or dysfunctions in the cell cycle and has an antitumor effect by inducing apoptosis [9, 10].

The purpose of this study was to determine the effect of CIS, a chemotherapeutic drug, on one of the AML cell lines, Kasumi-1, on cell proliferation, DNA repair, and cell cycle-related genes, as well as the expression changes of specific oncogene URG4/URGCP and DNA damage formation. In this context, the goal is to gain a better understanding of cisplatin's effects on these cells and shed light on potential therapeutic approaches.

Material and methods

Given that our research was conducted in an in vitro setting, it does not necessitate approval from an ethics committee.

Propagation of the Kasumi-1 cell line

The Kasumi-1 cell line was cultured in RPMI1640 medium. This medium contains 10% fetal bovine serum, 100 mg/ml streptomycin, 25 mM L-glutamine, and 100 IU/ml penicillin. The incubation was carried out in a humidified atmosphere of 95% and 5% CO_2 in an incubator at 37°C.

Cell viability test

To determine the IC50 value in the Kasumi-1 leukemia cell line, doses of CIS ranging from 2.5 µM to 160 µM were applied. The effects in this dose range were assessed depending on time and dose. Cell viability was determined using the CellTiter-Glo method, a sensitive luminometric method based on the measurement of ATP from living cells. This determination was conducted at time intervals of 24, 48, and 72 hours.

Total RNA and cDNA retrieval

To determine gene expression levels, total RNA isolation was performed in all groups, both control and dose, with the Trizol reagent. This isolation procedure was used to extract all of the RNA contained in the cells using the Trizol reagent. The reverse transcription procedure for cDNA synthesis was then performed. The "Transcriptor First Strand cDNA Synthesis Kit" was used to complete the reverse transcription procedure.

Real-time PCR analysis

The changes in mRNA expression levels of the genes p53, ATM, ATR, CHECK1, CHECK2, CDC25A, CDC25C, ERCC1, GADD45A, GADD45G, CCND1, CDK6, BAX, BCL-2, and URG4/URGCP were analyzed using the Real-Time PCR method. In this analysis method, gene-specific primers were used. The primer sequences of the genes examined in the study are shown in Table 1.

Table 1. Primer sequences of genes analyzed in real-time PCR

Gene Name	Base Sequences of Genes
p53	Forward 5′ATCTACAAGCAGTCACAGCACA3′
	Reverse 5′GTGGTACAGTCAGAGCCAACC3′
ATM	Forward 5'TGTTCCAGGACACGAAGGGAGA3'
	Reverse 5'CAGGGTTCTCAGCACTATGGGA3'
ATR	Forward 5'GGAGATTTCCTGAGCATGTTCGG3'
	Reverse 5'GGCTTCTTTACTCCAGACCAATC3'
CHECK1	Forward 5'GTGTCAGAGTCTCCCAGTGGAT3'
	Reverse 5'GTTCTGGCTGAGAACTGGAGTAC3'
CHECK2	Forward 5'GACCAAGAACCTGAGGAGCCTA3'
	Reverse 5'GGATCAGATGACAGCAGGAGTTC3'
CDC25A	Forward 5'TCTGGACAGCTCCTCTCGTCAT3'
	Reverse 5'ACTTCCAGGTGGAGACTCCTCT3'
CDC25C	Forward 5'AGAAGCCCATCGTCCCTTTGGA3'
	Reverse 5'GCAGGATACTGGTTCAGAGACC3'
ERCC1	Forward 5'GCTGGCTAAGATGTGTATCCTGG3'
	Reverse 5'ATCAGGAGGTCCGCTGGTTTCT3'
GADD45A	Forward 5'CTGGAGGAAGTGCTCAGCAAAG3'
	Reverse 5'AGAGCCACATCTCTGTCGTCGT3'
GADD45G	Forward 5'CGTCTACGAGTCAGCCAAAGTC3'
	Reverse 5'CGATGTCGTTCTCGCAGCAGAA3'
CCND1	Forward 5'AGCTCCTGTGCTGCGAAGTGGAAAC3'
	Reverse 5'AGTGTTCAATGAAATCGTGCGGGGT3'
CDK6	Forward 5'AGACCCAAGAAGCAGTGTGG3'
	Reverse 5'AAGGAGCAAGAGCATTCAGC3'
BAX	Forward 5'AGAGGATGATTGCCGCCGT3'
	Reverse 5'CAACCACCCTGGTCTTGGATC3'
BCL-2	Forward 5'TTGGCCCCCGTTGCTT3'
	Reverse 5'CGGTTATCGTACCCCGTTCTC3'
URG4/URGCP	Forward 5′CGGGAGATGGGACAGTTTTA3′
	Reverse 5′CATGGTGTTGAGGAGTGTGG3′

Comet assay method

The Comet Assay method was used to assess the DNA damage caused by CIS in Kasumi-1 cells. After applying the determined IC50 values to the cells, they were washed three times with 0.1M PBS. The cells were then treated with trypsin and removed from the Petri dishes. Three frosted glass slides were prepared for the control and CIS-treated dose groups. These slides were made by adding three layers of low melting point agarose gel at 37°C. After solidifying the first layer of 1.8% low melting point agarose gel, add 25 µL of sample and 1% low melting point agarose gel to the second layer. The third layer was filled with 1% low melting point agarose gel. The slides were incubated for 1 hour at +4°C in a pH-adjusted cold lysis solution with 1% Triton X-100, 100 mM EDTA, 10% DMSO, 2.5 M NaCl, and 10 mM Tris. The electrophoresis was conducted at 25 volts. After electrophoresis, the slides were washed in a solution adjusted to 0.4 M Tris; pH 7.5. They were then immersed in methanol at -20°C for five minutes and left to dry until the slides were dry. The emissions were observed at 590 nm while excitation filters were measured at 510/560 nm using a Nikon fluorescence microscope. Before examining under the microscope, all slides were exposed to ethidium bromide. The images of the comet tails were used at 20X magnification under the microscope [11].

Statistical analysis

The analysis of the data was conducted quantitatively using the ΔΔCT method through computer software. In this analysis, the web-based "RT² Profiler™ PCR Array Data Analysis" program was used, and Volcano Plot analyses were performed. The ΔΔCT method is based on the comparison of two expression results within ±3SD. With this method, the expression values of the relevant genes of the control and dose groups were determined relatively. Additionally, the comparison of the groups was statistically evaluated using the "Student t-test" analysis found in the "RT² Profiler™ PCR Array Data Analysis" program. For the determination of DNA damage, measurements were made using Comet Assay IV Version 4.3.2 for Basler FireWire.

Results

Cell viability

As a result of the conducted study, cell viability was initially determined by applying CIS to Kasumi-1 cells, one of the AML cell lines. The CellTiter-Glo kit, a luminometric method, was used to determine cell viability. Measurements were performed at 24, 48, and 72 hours, based on the application made to the cells used in the study. The effect of CIS on the Kasumi-1 cell line varied in a time- and dose-dependent manner. The IC50 value for the groups treated with CIS was determined to be 160 µM at 48 hours for the Kasumi-1 cell line. According to the results obtained, the distribution of CIS in Kasumi-1 cells depending on dose and time is shown in the graph below, Figure 2.

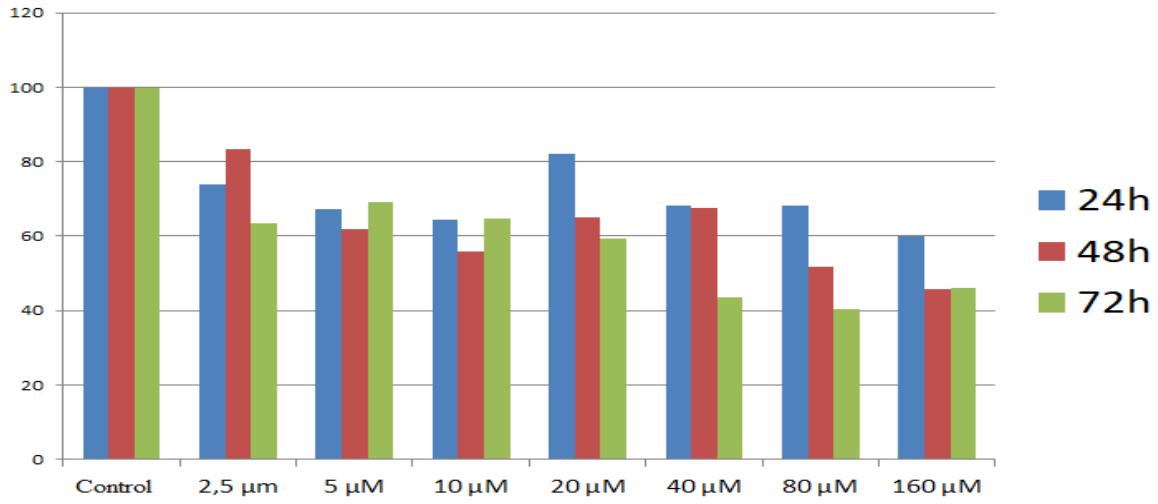

Figure 2. Percentages of cell viability in Kasumi-1 cells after CIS treatment based on time and dose

Real-time PCR analysis

cDNA synthesis was performed using the Transcriptor First Strand cDNA Synthesis Kit from the total RNAs obtained from the groups treated with CIS and the control group. Subsequently, the Real-Time PCR method was used to investigate the mRNA expression levels of the genes commonly known to be associated with apoptosis and the cell cycle, including p53, ATM, ATR, CHECK1, CHECK2, CDC25A, CDC25C, ERCC1, GADD45A, GADD45G, CCND1, CDK6, BAX, BCL-2, and URG4/URGCP. Based on the results obtained, significant results were found in the expression levels of the genes p53, BCL-2, CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G, and ATM. As no statistically significant difference was found in the results obtained for ATR, CHECK2, CDC25A, ERCC1, and BAX genes, they were not included in the graph (Figure 3).

Comet assay

The Comet assay was conducted to detect DNA damage in cells after treating the Kasumi-1 cell line with CIS for 48 hours at a dose of 160 µM. In the control group, it was observed that there was no DNA damage in Kasumi-1 cells, which appeared with a round shape (Figure 4). However, in Kasumi-1 cells treated with CIS, both the tail length and the percentage of DNA in the tail significantly increased in the dose group, as analyzed (Figure 5).

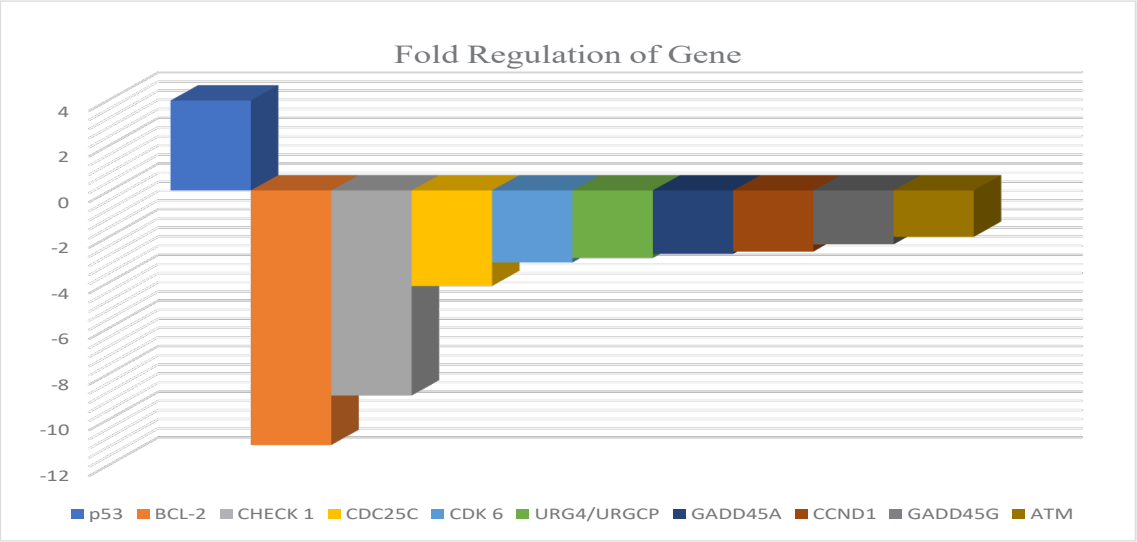

Figure 3. Fold Changes in the expression of p53, BCL-2, CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G, and ATM genes at the mRNA level in Kasumi-1 cell lines after CIS treatment

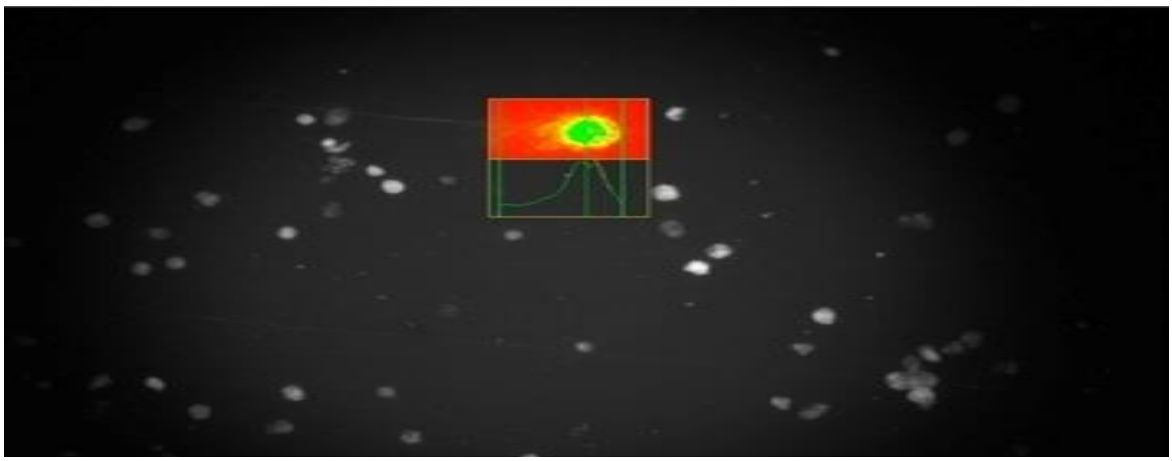

Figure 4. Comet assay result obtained from the control group

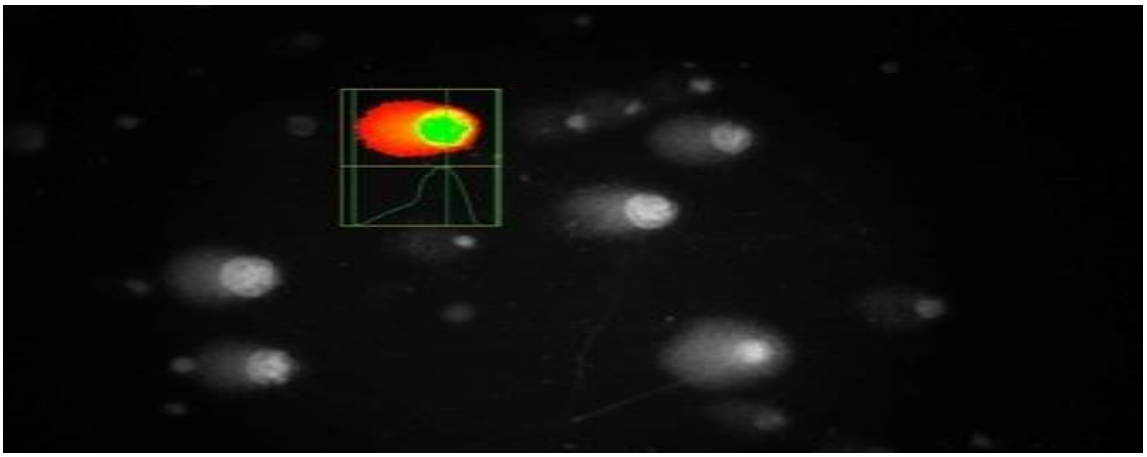

Figure 5. Comet assay result showing

Discussion

Leukemia is a type of cancer characterized by the abnormal and uncontrolled proliferation of blood cells [12, 13]. Another well-known form of this cancer type is AML cells. AML is a type of blood cancer that results from the uncontrolled proliferation of myeloid stem cells located in the bone marrow [14, 15]. This condition leads to genetic changes that cause the abnormal maturation of myeloid stem cells. AML cells can lead to the accumulation of abnormal cells in the blood, bone marrow, or sometimes other body tissues, which can cause various symptoms to appear [16, 17]. As with many cancer treatments, this cancer treatment usually involves processes with chemotherapy, radiotherapy, cell transplantation, or the use of different drugs [18]. The most commonly used treatment method is chemotherapy. In patients undergoing chemotherapy, the main goal is actually to heal the cancerous tissue and improve patient quality of life [19]. However, various chemotherapeutic drugs are used during the treatment process, and these drugs actually affect healthy proliferating cells outside the target tissue. So, as much as we want to achieve positive results with this method, we may also encounter more negative outcomes [20]. One of the chemotherapeutic agents that have been widely known and used for years in chemotherapy is CIS.

CIS, which goes by the chemical name cis/diamine/dichloro/platinum (II), is known as a platinum compound that hosts amine and chlorine atoms [21]. It was first found to have an antibacterial effect with the growth of Escherichia coli bacteria. Later, it was discovered to create an anti-neoplastic effect on cancer cells and entered the class of strong chemotherapeutic drugs used in cancer treatment [22]. This platinum-based drug is still widely used in the treatment of various cancers such as lymphoma, testicular, head-neck, ovarian, and cervical cancers [23]. When cisplatin enters the cells, it loses the chloride ligand and becomes activated. Once active, it forms covalent bonds with guanine bases in DNA [24]. These bonds cross-link the two strands of DNA, thereby inhibiting the normal function of DNA. This process, especially during cell division, inhibits DNA replication and transcription, stopping the proliferation of cancer cells. However, the DNA damage caused by cisplatin triggers the cell's repair mechanisms [25]. One of these repair mechanisms is the ATM pathway. The ATM pathway detects DNA damage, then stops the cell cycle and initiates DNA repair. This allows cells to recover from DNA damage, thereby ensuring cell survival. When the ATM pathway is activated, many genes responsible for stopping cell cycle growth such as the p21 gene, DNA damage-inducing gene 45 (GADD45) involved in DNA repair, and Bax/BCL-2 involved in apoptosis are activated [21, 26]

The aim of this study was to investigate the effect of CIS, a frequently used chemotherapeutic agent in chemotherapy, on the Kasumi-1 cell, one of the AML cells, on cell proliferation, cell cycle, and apoptotic genes, as well as the expression changes of the oncogene URG4/URGCP, and additionally, to examine its effects on DNA damage with comet analysis to show more clearly the role of CIS in DNA damage. Firstly, a cell viability test was conducted using the Celltiter-Glo kit.

Measurements were taken at 24, 48, and 72 hours following the application. According to the data obtained from the measurements in the study, the IC50 value in the groups where CIS was applied was determined as 160 μM at 48 hours in the Kasumi-1 cell line. Then, Real-Time PCR was performed to examine the mRNA expression levels of the p53, ATM, ATR, CHECK1, CHECK2, CDC25A, CDC25C, ERCC1, GADD45A, GADD45G, CCND1, CDK6, BAX, BCL-2, and URG4/URGCP genes. As a result of the PCR, significant results were obtained in the expression levels of the p53, BCL-2, CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G, and ATM genes. In the groups treated with CIS, a decrease in the mRNA expression level of the BCL-2 gene, which is effective in the apoptosis pathway, was detected. At the same time, an increase in the expression level of another apoptotic gene, p53, was observed. Many studies on CIS have found that the expression levels of the BCL-2 gene lead to different results in different cell lines [27, 28]. On the other hand, increases in the expression level of the p53 gene have been shown in different studies where CIS was applied [28-30]. In this regard, cell line in this study show similarities with the literature. Additionally, in the study, the expression levels of the CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G, and ATM genes, which are involved in the cell cycle, were examined. According to the results obtained, it was determined that the expression levels of these genes decreased. The low expression of these genes indicates that there are malfunctions in the cell cycle or even that the cell cycle is stopped. The effect of CIS has reduced the expression of these genes, and most of the studies in the literature show evidence that CIS is effective in the cell cycle [31-33]. Finally, comet analysis was conducted to detect DNA damage in the Kasumi-1 cell line with CIS. According to the data obtained from this analysis, no deformation was observed in the control group. However, in the cells treated with CIS, it was observed that the tail length and the percentage of DNA in the tail increased compared to the control group. Based on these results, we can say that DNA breaks occurred in the groups treated with CIS [34-37]. By investigating the mechanisms through which CIS induces changes in gene expression and DNA integrity, this study adds valuable insights into the broader understanding of chemotherapy's impacts, particularly in the treatment of leukemia with AML characteristics.

This study evaluated the mRNA levels of genes such as p53, BCL-2, CHECK 1, CDC25C, CDK 6, URG4/URGCP, GADD45A, CCND1, GADD45G, and ATM by examining the effects on DNA repair mechanisms, cell cycle mechanisms, and apoptotic genes in the Kasumi-1 cell line. Additionally, we identified the significant effects of CIS on the cell cycle and DNA repair mechanisms through analytical methods used to detect DNA breaks. The results of the comet assay also confirmed that CIS causes DNA breaks. The findings demonstrate that this study carries unique value and will serve as an important reference for future research. We hope that these findings will illuminate studies on the treatment and prevention of AML, a type of leukemia cancer, and will occupy a significant place in the literature.

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Authors contributions: Y.D. have constructed the main idea and hypothesis of the study. Y.D., M.S., L.E. and N.D. conducted experiments. Y.D., M.S., S.S., and U.P. analyzed data. Y.D., S.S. and Z.A. wrote the manuscript. In addition, all authors discussed the entire study and approved the final version.

Conflict of interest: No conflict of interest was declared by the authors.

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