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The Effect of Taxol on some Blood Parameters and Study of Histopathological Changes in the Kidneys of Laboratory Rats

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Abstract. Taxol is a microtubule inhibitor drug widely used in treatment of many types of cancer. In the present study Taxol at different doses if the rats were randomly divided into three groups, each group containing 12 laboratory rats, as follows: The control group consisted of 12 rats injected with 0.5 ml of distilled water. The low dose group consisted of 12 rats injected with 2 mg/kg of Taxol intraperitoneally. The high dose group consisted of 12 rats injected with 4 mg/kg of Taxol intraperitoneally. The results of histological examination of tissue sections showed pathological histological changes in the kidneys of laboratory rats. The results of the current study showed a significant decrease below the probability level of P≤0.05 in blood parameters including white blood cell count and percentage of lymphocytes, neutrophils, eosinophils and basophils in laboratory rats treated with (TAXOL) at two doses (2.4 mg/kg). The results of the study showed a significant decrease in the number of red blood cells below the probability level of P≤0.05 at both high and low doses, noting that the effect of the high dose was greater than the low dose. The results of histological sections of the kidneys of laboratory rats treated with Taxol showed blood congestion in the blood vessels with degenerations in the proximal and distal endothelial cells and atrophy of the renal glomeruli

Highlights:

1. Groups: Control, 2 mg/kg Taxol, 4 mg/kg Taxol (n=12/group).
2. Blood: Taxol reduced WBC, RBC, lymphocytes, neutrophils significantly (P≤0.05).
3. Kidney: Congestion, cell degeneration, glomerular atrophy observed in treated rats.

Keywords: Taxol, Chemotherapy, nephrotoxicity, Hematological

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Introduction

Cancer is an illness in which cells divide uncontrollably, resulting in the formation of neoplasms. Further, the cancer cells can devolve to other sites via blood vessels, sawing the cancer to other body parts. It is considered the second most malady that brings about mortality after cardiovascular illnesses globally. Also, it is mentioned that

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the rate of betterment and the chances of survival for various kinds of cancer with early detection is more than at a late time [1]. The use of chemicals in cancer treatment dates back several hundred years, but it was not until the 1940s that the rst successful and documented use of systemic chemotherapy took place. Based on warfare experience of toxic effects of nitrogen mustard on the lymphatic system, this agent was used for treatment of a patient with lymphoma. Although the tumors rapidly relapsed after an initial pronounced antitumor effect, this experience marked the beginning of chemotherapy of malignant tumors [2]. Although chemotherapy is beneficial in treating cancer and eliminating tumors, it has many disadvantages .one of these is that these drugs are not characterized by therapeutic specificity, as they do not distinguish between normal and cancerous cells. Unfortunately, no currently available agent meets this criterion [3]. Bone-marrow and reproductive organs are highly affected by chemotherapy because these tissues have high proliferative rates .the liver and kidneys are also the most sensitive organs to the cytotoxicity of anti cancer drugs [4]. Not all chemotherapy drugs cause the same side effects to the same extent, but rather it depends on many factors including the type of treatment, its timing and dose, in addition to the patient's health history. Chemotherapy chemicals are often given in sessions, with patients being asked to rest between sessions to regain strength [5].

Research Gap

Due to the increasing and diverse numbers of anti-cancer drugs and the negative effects they cause, to varying degrees, on the cells and organs of the human body, especially since the incidence of cancer in Iraq has begun to increase significantly during the past two decades, our study aimed to study the effect of the drug Taxol on some blood parameters and kidney tissue in healthy laboratory rats.

Methods

Experimental Animals

Thirty rats were purchased, weighing approximately 200-250 grams. Laboratory rats were housed in appropriately sized plastic cages, the floor of which was covered with sawdust, and the cages were cleaned and sterilized. The cages were placed in a

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temperature-controlled laboratory before the start of the experiment. The animals were left to acclimatize for ten days, ensuring that both water and feed were available.

Experimental Design

Female laboratory rats were divided into three groups, each group containing 12rats. The first group, the control group, received normal saline solution. The second group, the low dose group, consisted of 12rats injected with Taxol at a concentration of 2 mg/kg intraperitoneally for six weeks. The third group, the high dose group, consisted of 12 rats injected with Taxol at a concentration of 4 mg/kg intraperitoneally, given twice weekly for six weeks.

Blood and Tissue Samples Collection

The animals were anesthetized with ether after reaching the end of the specified time period for the experiment of six weeks. Blood was collected directly from the heart by cardiac puncture using medical syringes (5 ml). (3 ml) of the blood percentage was placed in tubes containing GEL TUBE evacuated from the air and left for an hour at room temperature until the blood clots. Then the serum was separated by centrifugation for 15 minutes / 3000 rpm. The serum was stored in small plastic tubes at a temperature of (-20) until the test was performed. The animal was fixed on a plastic plate using pins and a longitudinal incision was made in the abdominal side. The liver tissue was removed and washed in a saline solution to get rid of the blood and placed in formalin at a concentration of 10% and stored for a whole day

Statistical analysis

The data were analyzed statistically using the Statistical package for the social sciences (SPSS) Version 25 program and using One-way ANOVA to analyze the data and the means were compared using L.S.D test at a probability level of (0.05).

Result and Discussion

Results

Hematological Results

The analysis results showed a significant decrease below the 0.05 probability level in white blood cells, a significant decrease in the percentage of neutrophils, a

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significant decrease in the percentage of lymphocytes. The results also showed a significant decrease in the number of red blood cells, as showed in table 1.

Table 1: Effect of Taxol on hematological parameters

Groups	WBC	NEU	LYM	RBC
	Mean ± SD			
Control groups	8.47±0.76[a]	5.35±0.81[a]	4.80±0.55[a]	5.76±0.99[a]
Low dose of drug Taxol (2mg/kg)	4.57±0.52[b]	2.09±0.87[b]	2.94±0.48[b]	3.86±0.42[b]
High dose of drug Taxol(4mg/kg)	3.13±0.81[c]	0.99±0.62[c]	1.84±0.38[c]	1.97±0.63[c]
LSD	0.16	0.17	0.19	0.10

- Different letters indicate a significant difference below the probability level (0.05) between the treatments compared to the control.

Histological Effect

Histological study of kidney sections of the control group showed the presence of the outer cortex consisting of Bowman's capsule, glomerular capillaries, and renal tubules, as well as the inner medulla, which consists of the conductive ducts, in addition to the loop of Henle combined with the blood vessels to give the appearance of the inner medulla of the kidney, as well as the presence of the renal glomerulus and the distal and proximal tubules, as in the picture (1).

Histological study of the kidney tissue treated with a concentration of (2 mg) showed the occurrence of clear histological changes if blood congestion appeared in the blood vessels with degenerations in the proximal and distal lining cells, as well as the beginning of glomerular atrophy, as in the picture (2).

While the histological study treated with a concentration of (4 mg) showed an increase in the severity of the injury in terms of bleeding, congestion, and advanced atrophy of the renal glomeruli, as well as cell degeneration and necrosis, as in the picture (3).

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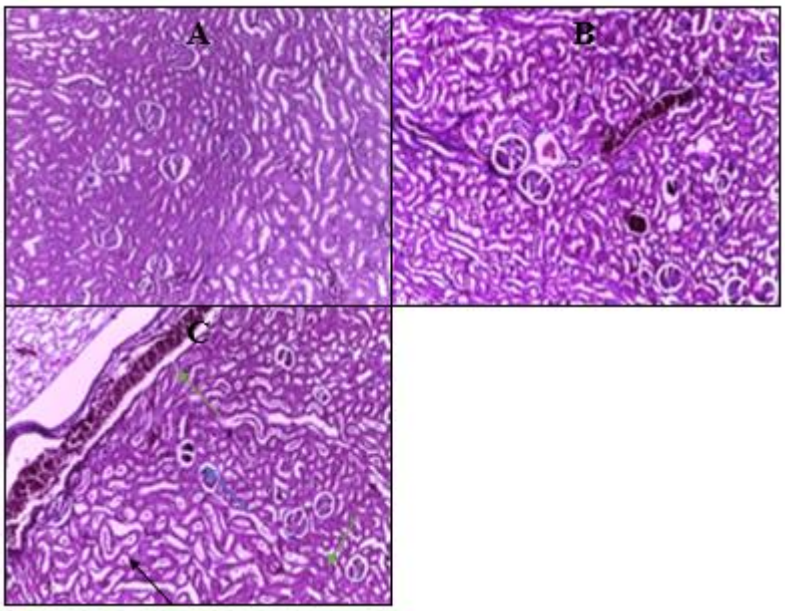

Figure 1: A: Histological section of the kidney of the control group showing the renal glomerulus (white arrow) and the renal tubule (blue arrow). B: Histological section of the kidney of rats treated with the low dose. Blood vessel congestion (black arrow), degeneration of proximal and distal endothelial cells (yellow arrow) and hemorrhage (red arrow) are observed. C: Histological section of the kidneys of rats treated with the high dose. Glomerular atrophy (green arrow), endothelial cell degeneration (yellow arrow), congestion (black arrow), and necrosis (orange arrow) are observed

Discussion

Effect of (TAXOL) on Hematological Parameters of Laboratory Rats

The results of the current study showed a significant decrease in blood parameters below the probability level (0.05) and at the two doses (2mg/kg-4mg/kg)) , as it showed a significant decrease in the total number of white blood cells, the percentage of lymphocytes, neutrophils, as well as the number of red blood cells The results of the current study were consistent with what was mentioned by [6], which showed that the drug Paclitaxel led to a decrease in blood parameters such as RBCs, Plate, Hb, and WBCs in cancer patients treated with this drug. This may be due to a deficiency in the hormone erythropoietin, which directly affects the bone marrow's production of blood parameters [7]. The decrease in blood parameters may be due to the effect of Paclitaxel, which is similar to Doxorubicin, on the epithelial cells of the

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kidney tubules and on the liver cells, which are responsible for the secretion of the red cell forming factor Erythropoietin, which plays a fundamental role in stimulating the bone marrow to form red cells and maintain them stable in the bloodstream [8]. The second reason for the decrease in this hormone is anemia resulting from renal failure [9]. The process of red blood cell production occurs under the influence of the erythropoietin factor secreted by the kidneys and is linked to globulin secreted by the liver to be the stimulating factor for the erythropoietin hormone, which carries it to the bone marrow and stimulates the stem cells to produce blood cells. If the renal-units are unable to secrete this hormone, it leads to renal anemia [10] Or the decrease in blood parameters is due to the anti-cancer drug generating free radicals, active oxygen O2 and hydrogen ions OH, which may lead to the hydrolysis of the unsaturated fatty acid chains that make up the phospholipids that are part of the cell membranes, thus affecting the synthesis of proteins represented by wall receptors, causing a defect in signal transmission leading to inhibition of the process of releasing transcription factors that lead to synthesis [11], or through the effect of free radicals oxygen Reactive species (ROS) that affected the process of division of red blood cell ancestors, which caused failure in the process of forming red blood cells and a decrease in their numbers [12], or perhaps the other reason for the decrease in blood parameters is the effect of the drug on inhibiting the mitotic division factor of bone marrow cells as is the case with other different drugs that lead to inhibition of blood cell generation [13]. The present study showed that neutrophil levels were significantly decreased in the post-chemotherapy phase compared to before chemotherapy. This result may be due to the fact that the myelosuppressive effect of chemotherapy on the marrow. Secondary neutropenia tends to be caused by chemotherapy drugs that are a specific reaction as an immune response or due to direct damage to the myeloid cell line [14]. In agreement with the result of our study, a previous study reported that the neutrophil level decreased. The neutrophil level decreased significantly in the post-chemotherapy phase. It was also reported that neutropenia occurs after the use of chemotherapy [15]. The present study also showed a decrease in the level of lymphocytes in the post-chemotherapy phase compared with that before chemotherapy. It was revealed that chemotherapy reduces the levels of circulating lymphocytes. The results of the present study contradict previous studies, which may be because the full extent of lymphocyte depletion was not visible until a

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large part of chemotherapy was completed. In contrast to this result, a previous study reported that lymphocyte levels were significantly decreased in the post-chemotherapy phase compared with that before chemotherapy [14].

Histopathological Effect of (TAXOL) on the Kidney of Laboratory Rats

One of the functions of the kidneys is to eliminate many drugs, including chemotherapy and their metabolites. The main pathways for the excretion of chemotherapeutic drugs through the kidneys: glomerular filtration and tubular secretion Glomerular filtration plays a major role with small molecules that are not bound to proteins of a size that can pass through the glomerular capillary wall These molecules cannot be filtered if they are bound to proteins in the bloodstream. These drugs, if secreted by the kidneys, enter the urine via secretion from the proximal tubule Chemotherapy agents can affect the glomeruli, tubules, interstitial, or renal microvasculature with clinical manifestations ranging from asymptomatic elevation of serum creatinine to acute renal failure requiring dialysis [16]. The only study on renal toxicity was that of [17], who performed a retrospective analysis of renal function in patients with gynecological cancers and found an increase in renal toxicity in patients treated with taxol and cisplatin compared to cisplatin alone. However, the literature on histological changes was not available. The present findings can be considered preliminary on this topic. In this study, it was observed that taxol administration leads to renal toxicity at both low and high therapeutic doses. A study of kidney tissue treated with a concentration of (2 mg/kg) showed clear tissue changes, with blood congestion appearing in the blood vessels, with degenerations in the proximal and distal endothelial cells, as well as the beginning of glomerular atrophy. While the histological study showed treatment with a concentration of (4 mg/kg) increased the severity of the injury in terms of bleeding, congestion, and advanced atrophy of the renal glomeruli, as well as cell degeneration and necrosis [18]. The tissue sections in the kidneys of the treated rats also showed the appearance of programmed cell death, and the reason is the drug (TAXOL) which caused an increase in the activity of free radicals ROS and thus the occurrence of programmed cell death in the renal tubules [19]. The tissue changes may be caused by the effect of nitric oxide (NO) on the cellular structures of the renal tissue. The study [20] indicated that treating laboratory rats with chemical drugs (TAXOL, 5FU) leads to an increase in the production of nitric oxide as a result of the increased

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expression of the gene for the enzyme inducible oxide synthase (iNOS), which leads to induce programmed cell death in tubule cells or due to the production of tumor necrosis factor α (TNF) [21]Or due to the combination of chemotherapy with DNA-forming nucleotides leading to DNA destruction and disintegration and thus the induction of programmed cell death [22]. A study by [23] indicated that treating laboratory rats with TAXOL increases the generation of free radicals, which leads to a decrease in the membrane potential of mitochondria in the renal tubules, which are the main and important source of energy for the renal tubules to perform their functions The expansion of Bowman's capsule space is attributed to a disturbance in the pressure inside and outside the capillaries, which leads to failure of the renal filtration process as a result of treating laboratory rats with the drug Doxorubicin [24].

Conflicts of Interest

The authors declare no conflict of interest.

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