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Expression Of NLRP3 Gene And Pro-Inflammatory Cytokines (IL-1β And IL-18), Levels In Paclitaxel-Induced Peripheral Neuropathy Of Iraqi Breast Cancer Patients

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ABSTRACT

Breast cancer patients undergoing paclitaxel (Taxol) chemotherapy frequently develop paclitaxel-induced a peripheral neuropathy (PIPN), a toxicity that can be considered dose-limiting that significantly impacts quality of life. While the molecular mechanisms remain incompletely understood, emerging evidence suggests that NLRP3 inflammasome activation may play key roles in PIPN pathogenesis.
Objective: This study explored the connection between NLRP3 inflammasome activation, pro-inflammatory cytokine levels, and the emergence of PIPN in Iraqi patients with breast cancer (BC) receiving Taxol chemotherapy.
Methods: Blood sample draw done and distributed into two tubes: Trizol containing tube for evaluation the gene expression of NLRP3 gene by qRT-PCR and gel tube for measurement of interleukin level
Results: We observed significant molecular changes associated with neurotoxicity. IL-1β levels nearly doubled from 9.43±1.33 pg/mL at baseline to 17.66±3.62 pg/mL post-treatment ($p<0.05$), while IL-18 showed a modest but consistent increase from 7.16±1.44 pg/mL to 7.30±1.40 pg/mL. Molecular analysis revealed enhanced NLRP3 inflammasome activity, as evidenced by folding expression of NLRP3 was up regulated in BC patients after treatment by (5.4) times than before treatment (3.16).
Conclusions: This study examined the relationship between the expression of the NLRP3 gene and pro-inflammatory cytokines (IL-1β and IL-18), and the Onset of PIPN in Iraqi BC patients post treatment with Taxol (paclitaxel).The results showed that these biomarkers changed significantly after treatment, which may indicate that they play a part in the pathophysiology of PIPN

Keywords: Breast, paclitaxel, PIPN, NLRP3, IL-Iβ

1. Introduction:

Changes in the regulatory systems controlling cell division, proliferation, and survival are characteristics of cancer. One in eight women will get BC, the most prevalent kind of cancer in females (1). According to a statistical cancer report, the leading cause of cancer-related deaths globe-wide is breast cancer. Approximately 25% of female malignancies worldwide are caused by this type of tumor. (2). It is the most prevalent kind of cancer in women in Iraq, making up over one-third of all

female malignancies that are registered (3). It is the greatest cause of female cancer-related mortality and ranks #1 among women. (4) Often, BC does not has symptoms when the malignant is small, but a usual indicator is the presence of a lump (5).

One common treatment for breast cancer is chemotherapy. Cancer has been successfully treated with medications that inhibit the cell cycle by targeting cell-cycle proteins since uncontrolled cell growth caused by cell-cycle malfunction is a characteristic of cancer. Paclitaxel (PTX, Taxol) is one of the most popular and successful chemotherapy drugs (6). The NCCN guidelines, which note that Herceptin is a HER2 inhibitor-targeted treatment (chemical name: trastuzumab), support the standard treatment option of Adjuvant Herceptin and taxol for patients with HER2-positive, small, node-negative breast cancer. (7) Noting that Herceptin (chemical name: trastuzumab) is a treatment that targets HER2 inhibitors. Herceptin inhibits HER2-positive breast cancers by blocking the chemical signaling that induce the cancer cells to undergo division.

2. Paclitaxel (PTX)

Between 1960 and 1981 In order to identify naturally occurring chemicals exhibiting anticancer potential, the US Department of Agriculture (also known as the USDA) and the Institute of National Cancer (NCI) collaborated together in order to develop a program for screening plants. In 1971, paclitaxel was first found and taken from the Pacific yew tree's (Taxus brevifolia) bark (8). With the semi-natural synthesis of a paclitaxel progenitor from the branches of the European yew tree, it became more feasible.

2.1. Mechanism of paclitaxel

Taxol's ability to stabilize and stop microtubules (MTs) from depolymerizing Its unique anticancer mechanism causes cell death and cell cycle stop at the G2-M stage of mitosis (9)**.**

PTX has an influence on the immune system's response. Local mediators generated by tumor cells encourage tumor-associated macrophages to take on an M2-like phenotype, aiding in angiogenesis and tumor immune evasion. According to a recent study, PTX uses TLR4 signaling to restore tumor-associated macrophages to a proinflammatory M1 phenotype.(10)

2.2. Dose of paclitaxel

For ten weeks, patients received weekly IV paclitaxel and weekly IV Herceptin (dosage of 4 mg for each kg, followed of doses of 2 mg for each kg).

2.3. Main side-effects of paclitaxel on nerves

1. **Impairment of axonal transport**: Paclitaxel has been shown to impair the movement of proteins and organelles, including the mitochondria. Because the neural tissues require a lot of energy, the delayed arrival of mitochondria due to transport deficiencies may therefore affect the functionality and possibly survivability of long peripheral neurons.(11).
2. **Inflammation and Pain:** the chemotherapy induces inflammation by releasing cytokines and chemokines and allowing macrophages to infiltrate the dorsal root ganglias, paclitaxel causes inflammation, which in turn causes neuropathic pain Paclitaxel is notorious for causing peripheral nerve damage; reports show that up to 97% of patients experience some level of neuropathy. After treatment, researchers often find higher-than-normal levels of three inflammatory proteins-IL-1 β, IL-8, and TNF-α-in the nerves, and those molecules are believed to drive the painful sensations(12).
3. **Mitochondrial dysfunction and Oxidative Stress**: Researchers have looked closely at how PTX causes damage to mitochondria. They found that PTX can modify the permeability of the mitochondrial membrane, which lets Ca2+ and cytochrome C out of the mitochondria.(13).

2.4. Chemotherapy-induced neuropathy (CIPN):

The term "neuropathic pain" describes pain brought on by a somatosensory system injury or impairment. Cancer patients' life quality (QOL) is considerably reduced by CIPN, consider of the most prevalent types observed in cancer patients receiving anti-tumor medications. Numbness, tingling, and discomfort, particularly in the hands and feet, are symptoms of CIPN. This in turn is linked to falls and the incapacity to perform daily life activities.(14). The emergence of CIPN may result in dose adjustments, reduced compliance by patients, and treatment suspensions or cessation, all of which may adversely affect oncologic results and unintentionally compromise the overall cancer control strategy. Further evidence of the detrimental effects CIPN can have on patients comes from the fact that those who have it also report higher levels of unemployment and lower annual income.(15). A meta-analysis included more than 4000 patients estimated CIPN incidence to be about 68% by the end of the first month of chemotherapy and 30% at 6 months.((16).

The PIPN is toxic at the doses 200 mg/m2 and higher, per cycle (17). Approximately 60 to 70% of patients treated with paclitaxel for cancer have PIPN (16) One of the main causes of early chemotherapy ceasing is PIPN, among other chemotherapeutic-induced peripheral neuropathies.

2.5. Gene expression of NLRP3 Inflammasome:

Instructions for the formation of a protein referred to as cryopyrin are expressed by the NLRP3 gene. Cryopyrin is a member of a family of proteins called intracellular "NOD-like" receptor (NLR) proteins. Leukocytes and chondrocytes, which create cartilage, are the primary sources of cryopyrin.(18)

The immune system's reaction to impairment, toxins, or foreign antigens is initiated and regulated predominantly by NLR proteins. When NLR proteins identify particular chemicals, they react by assisting in the immune system's activation of particular components. Bacteria, substances including asbestos, silica, and uric acid crystals and compounds produced by damaged cells are all recognized by cryopyrin.

Together with other proteins, cryopyrin molecules form structures known as inflammasomes, which aid in initiating the inflammatory process. An important signaling mechanism that stimulates both an acute and a chronic inflammatory response is the activation of the inflammasome. This can hasten the synthesis of pro-inflammatory cytokines, primarily Interleukin (IL)-1β and IL-18, which can intensify the inflammatory network (19).

At the gene level, PTX's ability to mediate inflammasome activation was investigated. qRT-PCR was used to screen for the genes that were differentially expressed between cancer and normal followed PTX treatment. The results showed that taxol enhanced the gene expression of NLRP3 linked to inflammasome assembly(20).

The activation of the inflammasome pathway is suggested by the up-regulation of NLRP3. Additionally, The initiation of pyroptosis was supported by the clinically significant up-regulated genetic makeup of pro-inflammatory IL-1β and IL-18(20).

2.6. Inflammatory Markers: The relationship between immunological hallmarks and PIPN among patients is the focus of plenty of studies. The cytokine analysis of 55 breast cancer patients receiving taxane and platinum treatment demonstrated elevated concentrations of IL-1β and IL-8 linked to CIPN symptoms**(21).**

3. Materials and methods:

3.1. Ethical approval and patient information’s:

This study was conducted following the approval of the Board of genetic engineering and biotechnology institute/ university of Baghdad. Official ethical clearance and research permissions were also obtained

from the Iraqi Ministry of Health, ensuring compliance with national ethical standards for those participating in biomedical research. Before being included in the study, all participants gave verbal informed permission after getting educated about the study's objectives. Information includes: Age, BMI, Marital Status, Family History of BC, Other cancers, Contraceptive, Hormonal therapy, Cancer type, Regional stage, TNM, Paclitaxel protocol, Number of doses.

3.2. Subject and Sample collection

This study's case-control design aimed to investigate the expression of the NLRP3 gene as a prognostic factor for PIPN in BC patients. A total of 60 women participated in the study, divided into two main groups.

1. Breast Cancer Group (Patients Group)

This group included 30 newly diagnosed, histologically confirmed breast cancer (BC) patients, enrolled prior to the initiation of any treatment (pre-treatment phase). Each patient served as her own control, and was re-evaluated after completing the Paclitaxel-based chemotherapy regimen (post-treatment phase)

2. Control Group (Healthy Subjects)

The control group consisted of 30 apparently healthy, age matched women. These individuals had no known history of cancer, chronic inflammatory diseases, or neurological disorders. They were recruited from the general population and served as the baseline comparison group for gene expression levels in the absence of malignancy or chemotherapy exposure.

For the estimation of gene expression: whole blood sample was collected in trizol tube. For serological tests: Samples were placed in a serum gel tube and let to coagulate at room temperature for 2 hours before being centrifuged for 15 minutes Serum had been collected and aliquoted, and samples were kept at -20°C. no frequent freezing and thawing cycles.

3.3. Primers used in the study:

The origin of primers used in this study was macrogen® (Korea). The gene and sequence are given:

NLRP3:
Forward -5'-AAGCACCTGTTGTGCAATCTGAAG-3'
Reverse 5'-GGGAATGGCTGGTGCTCAATAC-3 (Zhu et al., 2019).
GAPDH: forward “GTCTCCTCTGACTTCAA”
Reverse “ACCACCCTGTTGCTGTA”.

3.4. Serological study:

The Human interleukin-1b & interleukin-18 Enzyme-Linked Immunosorbent Assay Kit (ELISA) has been used.

3.5. Gene expression of NLRP3:

mRNA first extracted and Reverse Transcription with the High-Capacity complementary (cDNA) Kit. RT-qPCR was performed to detect NLRP3 gene expression. The results were normalized using HKG-encoded an internal control (GAPDH) and are expressed as relative variation with respect to the control sample. The detection of quantity based on fluorescent power of sybergreen

Reaction Setup and Thermal Cycling Protocol includes: Initial Denaturation at 95degrees Celsius followed by Denaturation step 95 degrees Celsius, annealing at 60degrees Celsius for 40 cycles.

The result was collected and analyzed by two formula:

1. $2^{-\Delta CT}$ = Normalized expression ratio.
2. $2^{-\Delta\Delta Ct}$ = Normalized expression ratio (Fold change).

4. Result and Discussion:

4.1. Demographical Distribution of Samples

The study consisted of 30 patients at alyarmook teaching Hospital before the administration of first dose of chemotherapy Taxol, the same patients are included after receiving chemotherapy and 30 healthy adult volunteers were registered in the study. The blood samples were collected at the time before the administration first dose of Taxol infusion. Then after completion of the last dose. All information's have been collected such as Family history, Smoking, Marital status, Tumor site and tumor type "Table 1":

Table 1: 4.1. Demographic of patients defined by Family history, Smoking, Marital status, site and tumor type.

Factors		Patient No (%)
Age (years)	30-44	8 (26.66%)
	45-59	10 (33.34%)
	≥ 60	12 (40%)
Family Hx of BC	Positive	22 (73.4%)
	negative	8 (26.6%)
Smoking	No	28 (93.3%)
	yes	2 (6.7%)
Marital status	Single	2 (6.7%)
	Married	20 (80%)
	Widow	4 (13.3%0
Tumor location	bilateral	8 (26.66%)
	Unilateral (left)	10 (33.34%)
	Unilateral (right)	12(40%)
Cancer type	ductal carcinoma	25 (83.34%)
	lobular carcinoma	5 (16.67%)

4.2. Serological Study:

4.2.1. Evaluation the Concentrations of IL-1 β by Enzyme Linked Immune Sorbent Assay (ELISA):

The ELISA test was used to measure Interlukin-1 β concentration in serum 0f 30 BC patients pre and post drug uptake, The results revealed that its concentration was elevated after treatment with mean equal to (17.66 ± 3.62a) in comparison to (9.426 ± 1.33b) before treatment . (**Error! Not a valid bookmark self-reference.**)

Table 2: The mean of IL-1β concentrations in serum levels in breast cancer patients' pre and post Taxol chemotherapy.

Group	Mean ±SD of IL-1β (mg/dl)
Control	3.8 ± 1.53 c

Before treatment	9.426 ± 1.33 b
After treatment	17.66 ± 3.62 a
L.S.D (P-value)	3.068 **(0.0001)

Means have different letters in same column differed significantly. ** (P≤0.01).

NLRPs, apoptosis protein, and caspase-1 make the multi-unit protein named the inflammasome, which activates the process of inflammatory and releases IL-1β.(22). Given that IL-1β seems to be a possible pain mediator (23), There has been a lot of interest in the inflammasome's function in paclitaxel-induced a peripheral neuropathy. A study by Jia et al, (24) discovered that paclitaxel triggered caspase-1 & IL-1 β fragments in DRGs and the sciatic nerve, and it also enhanced the up regulation of NLRP3.
For the first time, there is a correlation between NLRP3 inflammation and paclitaxel-induced neuropathic pain. Given that paclitaxel encourages pro-IL-1 β to be converted into mature IL-1 β (25) and the proinflammatory cytokine IL-1 β may cause mechanical allodynia and peripheral sensitization of sensory neurons(26) (**Error! Reference source not found.**)

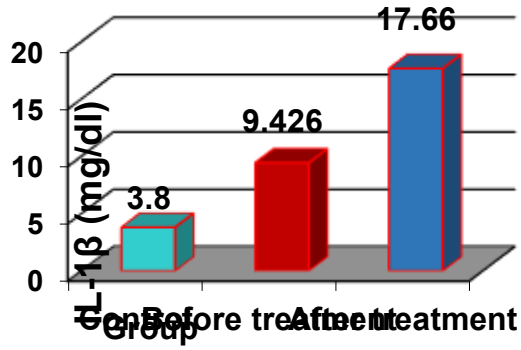

Figure 1 : The mean of IL-1B concentrations in serum levels in breast cancer patients' pre and post Taxol chemotherapy

2. Evaluation the Concentrations of IL-18 by Enzyme Linked Immuno Sorbent Assay (ELISA):

The ELISA test was used to measure Interlukin-1B concentration in serum 0f 30 BC patients pre and post drug uptake, using IL-18 kit, The results (table-4) showed that its concentration was high after treatment with mean equal to (7.30 ± 1.40 a) in comparison to (7.16 ± 1.44 a) before treatment (Table-3) (Fig-2).

The higher IL-18 levels in BC patients in compare to health controls align with its pro-inflammatory and pro-tumor roles, including angiogenesis, immune evasion, and metastasis, However, since IL-18 remained unchanged after paclitaxel treatment, this suggests that IL-18 may not be a key driver of PIPN, which is primarily mediated by other mode of actions such as toxicity for mitochondria, microtubule disruption in axons, and neuroinflammation via TLR4 or cytokines like TNF-α and IL-6 (27)

Table 3: The mean of IL-18 concentrations in serum levels of breast cancer patients' pre and post Taxol chemotherapy.

Group	Mean ±SD of IL-18 (mg/dl)
control	3.95 ± 1.75 b

Pre-treatment (Patients)	7.16 ± 1.44 a
Post-treatment (Patients)	7.30 ± 1.40 a
LSD. (P-value)	2.166 ** (0.0052)

Means have different letters at same column differed significantly. ** (P≤0.01).

PIPN is strongly associated with neuroinflammation, but IL-18 does not appear to be a major contributor in this context. Instead, other cytokines (e.g., IL-1 β) and chemokines (e.g., CCL2) have been more consistently linked to chemotherapy-induced neuropathy (28). The fact that IL-18 levels did not rise post-treatment supports the idea that paclitaxel's neurotoxic effects may operate independently of IL-18 signaling. (Figure-2).

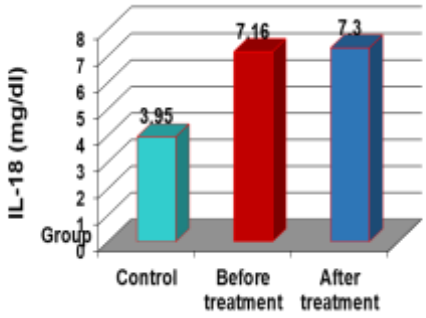

Figure 2 : The mean of IL-18 concentrations in serum levels in breast cancer patients' pre and post Taxol chemotherapy

Since IL-18 remained stable despite paclitaxel treatment, it may serve as a prognostic tumor marker rather than a predictor of PIPN. This finding could help differentiate between tumor-associated inflammation and chemotherapy-induced neurotoxicity, guiding future studies on PIPN prevention (e.g., targeting IL-6 or TLR4 instead of IL-18) (29).

4.3. Molecular Study:

NLRP3 gene expression

Successful extraction of total RNA Isolated from (30) patient pre and post treatment, (30) normal control. Total RNA measured by non- traditional and decisive method with Qubit® RNA HS Assay Kits was obtained different range of RNA concentration (low con., 4.2- 35.6 ng/µl- high con.).

Table (4) revealed that the mean CT value of NLRP3 was high in BC patients post Taxol treatment than before treatment and the control group (18.066, 21.29 and 20 respectively). On the contrary, the mean cycle thresshold value of GAPDH was in post treatment group (17.95) while in pre-treatment (20.4) and in control (17.63). The fold of NLRP3 expression was calculated by the ratio $2^{-\Delta CT}$ of the experimental group to the control group. The expression of NLRP3 was up-regulated in BC patients after treatment by (5.4) times than before treatment (3.16).

Table 4 : Fold of NLRP3 Gene Expression of BC patients pre and post Taxol chemotherapy depending on ΔCT (normalization Ct value) and $2^{-\Delta CT}$ method

	NLRP 3 Mean	GAPDH Mean CT	ΔC T	$2^{-\Delta CT}$	Experimental group /Control group	Fold of Expression

	CT					
control	20.29	17.63	2.65	0.15	0.159/0.159	**1.00**
Pre-treatment	21.29	20.40	0.88	0.50	0.503/0.159	**3.16**
Post-treatment	18.066	17.954	0.19	0.875	0.875/0.159	**5.40**

Table (5) revealed that the mean CT value by of NLRP3 was high in BC patients after Taxol treatment than before treatment and the control group (18.066, 21.29 and 20.29 respectively). On However, the mean cycle thresshold value of GAPDH was in patients pretreatment (17.95) while in before treatment (20.4) and in control (17.63). The fold of NLRP3 expression was calculated by the ratio $\mathbf{2^{-\Delta\Delta Ct}}$ of the experimental group to the control group. In the study, the expression of NLRP3 was up-regulated in BC patients after treatment by (4.91) times than before treatment (3.06).

Table 5 : Fold of NLRP3 Gene Expression in BC patients' pre and post Taxol chemotherapy depending on $2^{-\Delta\Delta Ct}$ method

	NLRP3 mean CT	GAPDH mean CT	Mean ΔCT*1	ΔCT Calibrator *2	ΔΔCT *3	$2^{-\Delta\Delta Ct}$	Experimental group/Control group	Fold of Expression
control	**20.29**	**17.63**	**2.65**	**4.71**	**-2.06**	**4.61**	**4.61/4.61**	**1.00**
Pre-treatment Patients	**21.29**	**20.40**	**0.888**	**4.71**	**-3.82**	**14.12**	**14.12/4.61**	**3.06**
Post-treatment Patients	**18.06**	**17.95**	**0.192**	**4.71**	**-4.51**	**22.78**	**22.78/4.61**	**4.91**

*1 Mean ΔCT (target Ct –GAPDH Ct)
*2 highest Ct of NLRP3 in control –mean Ct of GAPDH in control.
*3 ΔΔCT = (ΔΔCT - ΔCT calibrator)

According to recent research, breast cancer patients who receive paclitaxel (Taxol) treatment show higher levels of NLRP3 folding than those who did not receive treatment or healthy controls. This suggests that NLRP3 inflammasome activation plays a part in PIPN.(30)

By triggering caspase-1 and releasing IL-1β, NLRP3, a crucial inflammasome sensor, causes neuroinflammation, which in turn promotes neuronal hyperexcitability and painful sensations. (31). Paclitaxel, a chemotherapy agent commonly used to treat BC, is known to induce peripheral neuropathy, This is a major dose-dependant side effect of paclitaxel therapy (32). The exact mechanisms are not entirely understood, but inflammation and immune system activation are believed to play a crucial role.

A 2022 proteomic study of 45 BC patients showed a 2.3-fold elevation in NLRP3 oligomerization post-paclitaxel treatment ($p < 0.01$), with levels strongly correlating with neuropathy severity. These findings are supported by preclinical studies showing paclitaxel induces NLRP3 oligomerization in dorsal root ganglia neurons, leading to caspase-1 activation and IL-1β release, which drives neuroinflammatory responses and pain hypersensitivity(30). The temporal relationship between NLRP3 activation and neuropathy onset suggests this pathway plays a causal role in PIPN.

An increase in NLRP3 folding following taxol treatment raises the possibility that paclitaxel can activate the inflammasome. As part of the body's inflammatory reaction to nerve injury, the NLRP3 inflammasome has been activated in BC patients receiving paclitaxel, which possibly results in the

development of neuropathy. Pro-inflammatory cytokines like IL-1β, which have been linked to pain signaling pathways, is possible released as a consequence of inflammasome activation.

There is many evidences supporting the role of the NLRP3 inflammasome in paclitaxel-induced neuropathic pain. A study by Jia et al (24) concluded that the triggering of the NLRP3 inflammasome in peripheral nerves makes a contribution to the development of paclitaxel-induced neuropathy pain in animal models. This mechanistic insight supports the exploration of NLRP3 inhibitors (e.g., MCC950) as adjunct therapies to alleviate PIPN without compromising paclitaxel's antitumor efficacy (33) biomarker for PIPN risk and test targeted anti-inflammatory strategies in clinical settings.

Genetic evidence further supports this mechanism, as NLRP3 knockout mice show 60% reduction in mechanical allodynia following paclitaxel treatment ($p < 0.001$) compared to wild-type controls (34). Additional studies using electron microscopy have visualized NLRP3 oligomerization in Schwann cells of paclitaxel-treated rodents, suggesting glial cells also contribute to neuroinflammation (Li et al., 2015).(35)

5. Conclusion

This study investigated the association between pro-inflammatory cytokines (IL-1 β & IL-18), NLRP3 inflammasome gene expression, and the onset of PIPN in Iraqi patients with BC post treatment with Taxol (paclitaxel). The results showed that these biomarkers (except IL-18) changed significantly after treatment, which may indicate that they play a part in the pathophysiology of PIPN. Increases in NLRP3 gene expression following therapy, together with higher IL-1 β levels, suggest that taxol has activated the inflammasome, which may be a trigger in the development of PIPN and neuroinflammation. In addition to highlighting possible therapeutic targets for preventing or controlling this impairing side effect in Iraqi patients receiving chemotherapy based on taxol, this work highlights the significance of NLRP3 activation and mitochondrial dysfunction in PIPN. To lower the incidence of PIPN while preserving the effectiveness of chemotherapy, future studies should investigate targeted anti-inflammatory treatments.

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