EFFECTIVENESS AND SAFETY OF PLATINUM BASED AGENTS NEOADJUVANT CHEMOTHERAPY ON PATHOLOGICAL COMPLETE RESPONSE IN TRIPLE NEGATIVE BREAST CANCER PATIENTS (A RETROSPECTIVE STUDY)

Ahmed A. Elnaggar [1], Sohier S. Ismail[2], Sherif F. Elzawawy[3], Reham M. Faheim[2] and Khaled N. Abdelhakim[2]

[1] Department of Clinical Oncology, Faculty of medicine Tanta University, Tanta, Egypt
[2]Department of Clinical Oncology and Nuclear Medicine, Faculty of medicine, Ain Shams University, Cairo, Egypt
[3]Department of Clinical Oncology and Nuclear Medicine, Faculty of medicine Alexandria University, Alexandria, Egypt

Corresponding author:
Ahmed Abdel Aziz Elnaggar
Mobile: +2 01008118088
E-mail:
ahmednaggar89@gmail.com

Received: 16/04/2024
Accepted: 29/05/2024

Online ISSN: 2735-3540

ABSTRACT:

Background: *Triple-negative breast cancer (TNBC) is highly aggressive with mortality rates higher than hormone-positive because of the shortage of applied therapy. The main approach for TNBC patients was the neoadjuvant chemotherapy (NACT) to achieve pathological complete response (pCR). The ultimate goal of pCR is to improve local outcomes, event-free and overall survival (OS). adding platinum-based agents to NACT showing promising activity in achieving pCR in TNBC.*

Study objective: *To stand out the role of adding platinum-based agents to NACT in enhancing pCR rates in TNBC patients. Also, to evaluate the safety of platinum-based agents concerning complications.*

Materials and Method: *Retrospective study comprised medical records from 80 TNBC patients divided into 2 groups (40/group) treated with NACT either platinum free or platinum-based protocol from 2017 to 2022 at oncology department of both Ain shams and Alexandria university hospitals.*

Results: *Median age was 48.5. 50% were postmenopausal. 55% of the patients were T3, T4. 45% had positive LNS. pCR rates were favourable in platinum-based group, 17 patients (42.5%) achieved pCR, 23 patients (57.5%) had residuals while in platinum-free group, 9 patients (22.5%) achieved pCR, 31 patients (77.5%) had residuals with significant difference assessment by Pearson's Chi-square Test=3.647, P=0.047.*

Platinum based group had higher incidence of grade 3,4 complications than platinum free group shown with odds ratio 2.17 in thrombocytopenia, 3 in nausea and vomiting, lastly 5.57 in nephropathy.

Conclusion: *In TNBC patients, adding platinums to NACT is associated with higher pCR rates with mild complications so it may be considered an optional treatment.*

Keywords: *Breast cancer, Triple negative, pCR, Neoadjuvant, Platinum based agents.*

INTRODUCTION:

Breast cancer is a heterogeneous and hormone dependent malignancy, representing more than 20% of total female cancers. It is the most prevalent cancer in females, and after lung cancer, it is the second common cause of cancer-related deaths in females [(1)]. TNBC is a specific phenotype

characterized by lack of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2) [(2)]. TNBC represent about 20% of all breast tumours [(3)].

Although TNBC is more aggressive with rapid disease progression, early relapse, distant metastasis, poorer prognosis, higher mortality rates, and shortage of treatment options, but it has good response to chemotherapy which is called triple negative paradox [(4)]. Chemotherapy has been the most known systemic approach for TNBC. Neoadjuvant chemotherapy has been accepted standard therapy for patients with unresectable and respectable tumours. Concerning unresecatable tumours it may find a surgical solution through shrinkage of the tumour and downstaging of the disease, and in resectable tumour, it can be used to improve locoregional control and increased the rate of conservative surgery [(5)].

In the neoadjuvant approach, TNBC patients tend to achieve higher rates of response to standard chemotherapy in comparison with other breast cancer subtypes like hormone positive breast cancer patients. The standard neoadjuvant chemotherapy included anthracyclines plus cyclophosphamide followed by taxanes [(6)].

Pathological complete response (pCR) is pathologically described as absent invasive cancer in breast tissue and axillary LNS (ypt0/ypn0). pCR is widely used now as a potential endpoint for long-term results in the neoadjuvant chemotherapy of breast cancer [(7)]. The ultimate goal of pCR is to enhance local outcomes, event-free and overall survival (OS).

Reaching pCR in TNBC patients has a favourable value as patients who attain pCR have very good prognosis with rising rates of disease-free survival and overall survival that make them comparable to those with less aggressive tumor. However, TNBC patients with failure of reaching pCR have worse survival and prognosis [(8)]. About 30-40% of TNBC patients obtain pCR after standard neoadjuvant chemotherapy [(9)]. So neoadjuvant chemotherapy has been considered the most successful management for the most of TNBC patients [(10)].

Platinum based agents are cytotoxic damaging substances to DNA result in DNA strands break and consequently programmed cell death [(11)]. This mode of action makes them particularly effective against tumor cells that lack DNA repair mechanism. More than half of TNBC have homologous DNA recombinant defects that make them more sensitive to platinum damage [(12)]. Based on the biological rationale for tendency of TNBC to DNA destroying elements like platinum-based agents, several studies had tested the possible role of adding platinum-based agents to the neoadjuvant chemotherapy for TNBC patients to improve pCR rates and may affect the survival [(13-15)].

AIM OF THE WORK:

primary to evaluate the effectiveness of platinum based in comparison with platinum free neoadjuvant chemotherapy in TNBC patients, concerning pCR rates, and secondary to assess the safety of platinum based versus platinum free neoadjuvant chemotherapy in TNBC concerning complications (haematological and non-haematological).

METHODS OF THE STUDY:

Study design:

This study was retrospective study comprised medical records from 80 TNBC patients divided into 2 groups (40 patient for each group) treated with NACT either platinum free (group 1) or platinum-based (group 2) protocol from 2017 to 2022 at oncology department of both Ain shams university hospital and Alexandria university hospital.

Study population:

Inclusion criteria: Triple negative Female Patients with -ve ER, -ve PR, and -ve HER2. Their age at presentation was from 18 up to 70 years old. All patient was non metastatic and diagnosed with Stage I, II and III diseases including (locally advanced disease and inflammatory breast cancer disease).

Exclusion criteria: Patients who were more than 70 years old, with breast subtypes other than TNBC i.e., hormonal +ve or HER 2 +ve. Also, patients with metastatic disease, and Pregnant or lactating women.

Study procedures:

Patients eligible for study were breast cancer female patients diagnosed in the period between Jan 2017 to Dec 2022 at Ain Shams University Hospital and Alexandria University Hospital in Oncology Department. they had gone for the following steps *before starting systemic therapy:*

- Biopsy was taken reveals stage I, II and III breast cancer.
- Immunohistochemistry was triple -ve (-ve ER, -ve PR, -ve HER2).
- Metastatic work up was done and revealed no metastasis.
- Mammogram and breast ultrasound were done to asses tumour, LNs size and extension

Systemic Treatment:

The selected patients received neoadjuvant systemic chemotherapy either platinum free or platinum based.

Concerning platinum free: These patients received (anthracyclines plus alkylating agents followed by taxanes) as follow:

4 cycles AC (doxorubicin plus cyclo-phosphamide) cycle every 21 days, followed by 4 cycles taxanes (paclitaxel) (docetaxel) cycle every 21 days.

Concerning platinum based: These patients received the same protocol plus adding platinum-based agents (carboplatin or cisplatin) to taxanes.

Doses of the drugs were:

(Doxorubicin 60 mg/m^2)-(Cyclophosphamide 600mg/m^2)-(Paclitaxel 175mg/m^2)-(Docetaxel 75mg/m^2)-(Carboplatin AUC 5)-(cisplatin 75mg/m2)

Complication Assessment:

Assessment of adverse effects of the chemotherapy [16] happened to patients during period of treatment as:

Hematological complications as (neutropenia, thrombocytopenia and anemia [17] and non-hematological complications: Nephrotoxicity [18], Ototoxicity Neurological complications (peripheral neuropathy) [19], GIT complications (nausea, vomiting, diarrhea, oral mucositis) [20]. And if patient admitted to hospital with these complications.

Clinical and Radiological Review:

Review of the clinical examination data and radiological results of US or Mammogram done at the end of systemic chemotherapy.

According to RECIST criteria [21]:

Complete Response (CR): Is the absence of any primary tumours found either clinically or radiologically.

Partial Response (PR): Is when the total diameters of the breast tumours reduce by greater than 30%.

Progressive Disease (PD): Is characterised by a rise in breast tumour diameters of more than 20% as compared to the lowest total at the time of clinical diagnosis.

Stable Disease (SD): Defined as tumour size change between PR and PD.

Surgery:

The selected Patients after they finished systemic chemotherapy and underwent suitable surgery either mastectomy or breast conservative surgery depending on the clinical and radiological assessment.

Pathological assessment:

Assessment of the collected data obtained from the pathologist after surgery. all surgical pathology reports were centrally reviewed by the principal investigators. pCR is pathologically defined as absence of invasive cancer in the breast tissue and axillary LNS (ypt0/ypn0).

Ethical consideration:

This research was accepted via the Research Ethics Committee of the faculty of Medicine Ain Shams university (FWA 000017585- FMASU MS 531/2023). Nonidentification of the patient data form was signed.

RESULTS:

In the present study, the classification of the studied groups. Where platinum-free patients were 40 (50%), and the same in platinum-based carboplatin patients were 40 (50%). As presented in figure (1).

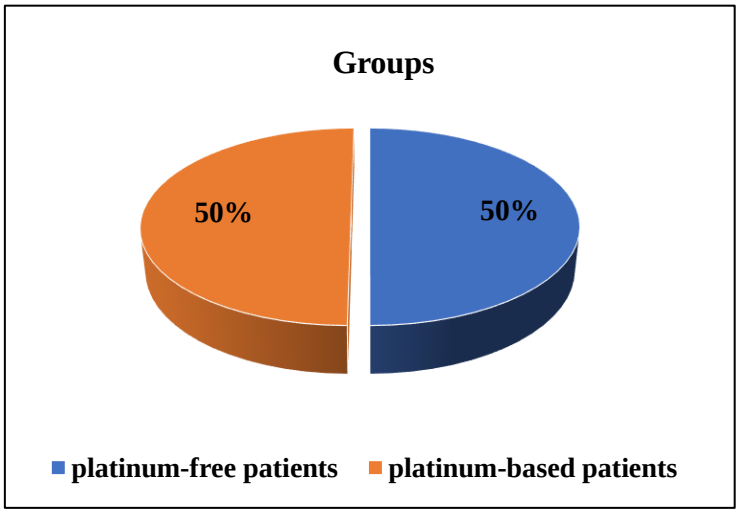


Figure 1: Classification of the studied groups

In platinum-free, the age of patients was from 28-69 y with a mean value of 48.3±11.85 and median 48.5, while in platinum-based patients, it ranged between 27-68 y with the mean value of 47.8±10.84 and median 48.5. There's no statistically significant difference in age between groups by Student-t test=0.197 and p=0.844. As presented in Table (1).

Table 1: Distribution of the studied sample according to age in relation to groups.

AGE / GROUPS	Range	Median (IQR)	Mean± SD	Student-t test	P value
platinum-free patients n=40	28-69	48.5 (36.75-58)	48.3±11.85	0.197	0.844
platinum-based patients n=40	27-68	48.5 (39.25-55.00)	47.8±10.84		

There were 23 (57.5%) patients in early stage in platinum-free group and 17 (42.5%) in locally advanced stage, while in platinum-based group; 17 (42.5%) in early stage and 23 (57%) were in locally advanced stage. There's no statistically significant difference between groups in relation to stage classification by Pearson's Chi-Square Test =1.800 (P value =0.263). As presented in Table (2).

Table 2: Classification of the studied groups according to stage and tumour extension

The studied groups	platinum-free patients n=40		platinum-based patients n=40	
	Number	Percent	Number	Percent
Stages classification				
Early stage (n=40)	23	57.5	17	42.5
Locally advanced (n=40)	17	42.5	23	57.5
Pearson's Chi-Square Test=1.800		P=0.263		

Concerning tumor size and LNS size reduction, There's a high statistically significant difference in tumor size reduction between groups after treatment by chemotherapy by independent Student-t test=2.892, and (P value =0.005). While There's a statistically significant difference in LNs size reduction between groups after treatment by chemotherapy by independent Student-t test=2.006, and (P value = 0.048). As presented in Table (3).

Table 3: Comparison of the percentage (%) of decrease in tumour and LNs size between the two groups

% Of change / GROUPS	Student-t test	P value
Tumor size		
platinum-free patients n=40	2.892	0.005**
platinum-based patients n=40		
LNs size		
platinum-free patients n=40	2.006	0.048*
platinum-based patients n=40		

Regarding radiological assessment after chemotherapy (RECIST criteria), in platinum-free patients, 9 (22.5%) had complete radiological response, 31 (77.5%) had non-complete radiological response while in platinum-based patients, 18 (45%) had complete response, 22 (55%) had non-complete response. There's a statistically significant difference between groups concerning RECIST criteria by Fisher-Freeman-Halton Exact Test=5.673 (P value =0.054). As presented in Table (4).

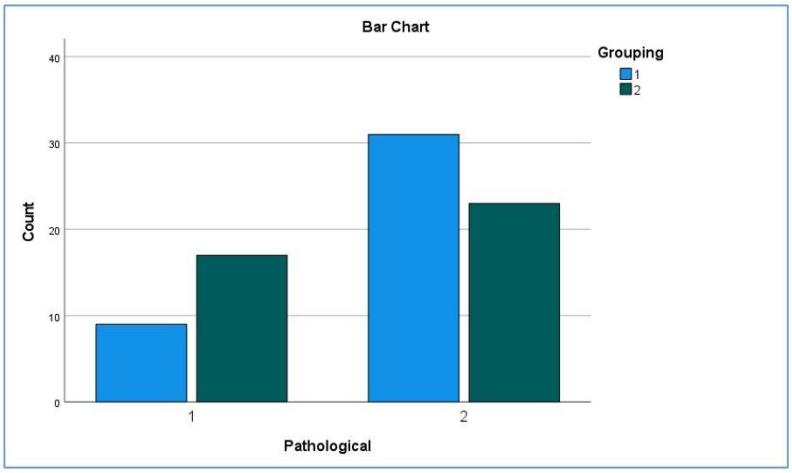
Table 4: Classification of the studied groups according to radiological assessment after NACT (RECIST CRITERIA)

The studied groups	platinum-free patients n=40		platinum-based patients n=40	
	Number	Percent	Number	Percent
Radiological assessment after chemotherapy (RECIST criteria):				
Complete response	9	22.5	18	45
Non-complete response	31	77.5	22	55
Partial response	24	60.0	19	47.5
Stable disease	6	15.0	2	5.0
Progressive disease	1	2.5	1	2.5
Fisher-Freeman-Halton Exact Test=4.528		P=0.054*		

According to pathological assessment after surgery, in platinum-free patients, 9 patients (22.5%) had no residuals (achieve pathological complete response pCR), 31 patient (77.5%) had residuals. while in platinum-based patients, 17 patients (42.5%) had no residuals (achieve pathological complete response pCR), 23 patients (57.5%) had residuals. There's a statistically significant difference between groups concerning pathological assessment by Pearson's Chi-square Test=3.647, (P value =0.047). As presented in Table (5) and Figure (2).

Table 5: Classification of the studied groups according to pathological assessment after surgery (pCR)

The studied groups	platinum-free patients n=40		platinum-based patients n=40	
	Number	Percent	Number	Percent
pathological assessment after surgery:				
No residual	9	22.5	17	42.5
Residual	31	77.5	23	57.5
Pearson's Chi-square Test=3.647		P=0.047*		



1=residual, 2=no-residual

Figure 2: Classification of the studied groups according to pathological assessment after surgery

According to Relation between grade 3 and 4 complications of the studied group of patients and platinum usage as a part of chemotherapy with odds ratio (CI).

Platinum based group had higher incidence of grade 3,4 haematological complications than platinum free group with odds ratio 1.76 in anaemia, 2 for neutropenia and 2.17 in thrombocytopenia, also higher grade 3,4 non-haematological complications was shown with odds ratio 1.13 in peripheral neuropathy, 1.58 in mucositis, 3 in nausea and vomiting, lastly 5.57 in nephropathy. as presented in Figure (3).

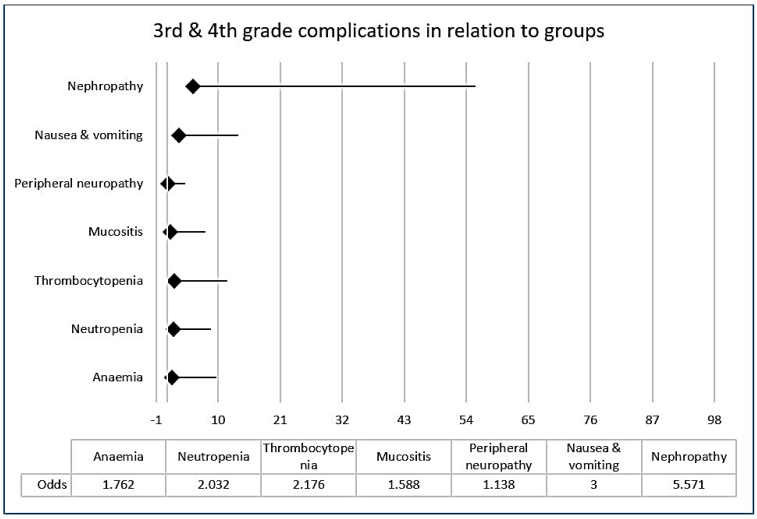


Figure 3: Relation between grade 3,4 complications of the studied group of patients and platinum usage as a part of NACT calculated with odds ratio (CI)

Stastical analysis [22]:

Data were fed to the computer and analyzed using IBM SPSS software package version 27.0**. (**Armonk, NY: IBM Corp**)** [23] Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean and standard deviation. The significance of the obtained results was judged at the 5% level.

The used tests were:

1.Student t-test independent sample:

For testing significance between parametric ≥30 quantitative variables in two studied groups.

2.Fisher-Freeman-Halton Exact Test:

For categorical variables when >20% of cells with 5 value or less, to compare between different groups.

3.Pearson's Chi-square test (*$\chi 2$*):

For categorical variables when ≤20% of cells with 5 value or less, to compare between different groups.

4.Paired t-test:

For testing significance between parametric quantitative variables in two groups in two different times.

DISCUSSION:

(pCR) is considered the gold standard of outcome and survival. Several studies have illustrated the favourable relation between (pCR) and outcome [7&8&24-26]. All these studies conclude that obtaining (pCR) improve local outcomes as well as event-free and overall survival. in our study we show the increased PCR rates after adding platinum-based agents to NACT in TNBC patients whatever the platinum-based agent used either carboplatin or cisplatin. As more than half of TNBC have homologous DNA recombinant defects that make them more sensitive to platinum damage.

In our study pCR rates increased by about 20% (42.5% for platinum-based group versus 22.5% in platinum free control group) with significant difference by Pearson's Chi-square Test=3.647, (P value =0.047) and this is consistent with the findings by various studies:

The meta-analysis performed by *Li and his colleagues* in 2020 [15] showed that adding platinums to standard chemotherapy increase the rate of pCR by 13.2% (49.1% in the platinum based NACT group vs. 35.9% in the standard NACT group). but in a study by *Gass and colleagues* in 2018 [27], pCR reached 50% after platinum-taxanes protocol (*vs.* 41.8% after anthracycline-taxanes protocol). Similarly, in the GeparSixto trial in 2014 [14], carboplatin-based NACT increased pCR rates – 53.2% *vs.* 36.9% ($p = 0.005$).

In meta-analysis by *Petrelli et al.* in 2010 [28], the pooled pCR rate for 1,598 patients with TNBC treated with platinum based NACT was 45%. *Poggio et al.* in 2018(13) also reported a significantly increased pCR rate 51% in patients with TNBC received platinum based NACT. *Ando et al.* in 2015 [29] found the highest pCR rate that reached 61% for those treated with anthracycline followed by taxanes plus carboplatin.

Randomized phase II study performed by JOVANOVIĆ, *Bojana, et al.* in 2017 [30] showed increase in pCR rates up to 49% after adding cisplatin to taxanes in neoadjuvant setting but 36% in control group. A retrospective study performed by HUANG, *Liang, et al.* in 2017 [31] to compare between cisplatin and carboplatin in neoadjuvant therapy showed close results in pCR rates between the two platinum agents (44% in cisplatin group and 42% in carboplatin group)

On the contrary of our results, the earlier GEICAM randomized trial in 2006 showed no improvement in pCR rate with

carboplatin [32]. As the patients in this study received alkylating agent before platinum-based NACT. So, it may be a previous chemotherapeutic agent that cause DNA damaging may decrease the benefits from adding of a platinum compound to standard NACT.

NACT protocols include anthracyclines and taxanes already increase the risk of myelosuppression (anemia-neutropenia-thrombocytopenia) addition of platinum-based agents has slight risk of increase myelosuppression. And may increase the risk of grade 3,4 hematological and non-hematological complications.

In our study complication were slightly similar, Grade 3,4 Haematological complications were approximately similar concerning anaemia but more for thrombocytopenia and neutropenia Odds Ratio 2.17 and 2 respectively. Grade 3,4 non haematological complications were approximately similar concerning peripheral neuropathy and mucositis but more for (nausea, vomiting) and nephropathy Odds Ratio 3 and 5.57 respectively.

Various studies reported different grades of complications ranged from slightly increased complication to aggressive grade 3,4 complication that required hospital admission. *Sikov WM et al.* [33] reported increased risk of grade 3,4 neutropenia and thrombocytopenia after adding carboplatin to NACT which led to delay in receiving cycles. *Gluz O et al.* [34] reported increase in neutropenia up to 11.7% versus 3.3%.

Ando M et al. [29] reported in a study included 88 patients treated with carboplatin added to paclitaxel, 65 patients (73.9 %) required delaying or at least reduction of paclitaxel dose, also 18 patient required reduction of carboplatin dose. From 91 patients treated with platinum, 28 patients (30.8 %) required delaying or at least reduction of paclitaxel dose. *Zhang P et al.* [35] reposted slight increased risk of thrombocytopenia up to 3.5%. While the results from GEICAM/2006-03, multicentre study 2012 [32] don't found any significant difference in grade 3,4 adverse effects in both groups.

A recent meta-analysis done by *Poggio et al.* [13] reported decreased rates of grade 3,4 peripheral neuropathy in platinum-based and platinum-free NACT for TNBC (3.6% in both groups). *Yang R et al.* [36] reported increased risk of nausea and vomiting in platinum-based arm in comparison to platinum free arm with odds ratio 2.22.

Conclusion:

In patients with TNBC, adding platinum compounds to NACT is associated with higher rates of pCR with mild complications so it may be considered as an optional treatment.

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فعالية وسلامة إضافة مركبات البلاتين إلي العلاج الكيميائي التمهيدي ماقبل الجراحة وتأثيره علي الإستجابة الباثولوجية الكاملة في مرضي سرطان الثدي الثلاثي السلبية (الخلايا الصلعاء)

أحمد عبد العزيز النجار[1]، سهير سيد إسماعيل[2] ، شريف فاروق الزواوي[3] ، ريهام محمد فهيم[2] ، خالد نجيب عبد الحكيم[2]

قسم الاورام والطب النووى- الكلية الطب جامعة طنطا [1]
قسم الأورام والطب النووي – كليه الطب - جامعة عين شمس[2]
قسم الأورام والطب النووي – كليه الطب - جامعة الإسكندرية [3]

الخلفية: يرتبط سرطان الثدي الثلاثي السلبية للمستقبلات الهرمونية بشراسة مرضية أعلى من سرطان الثدي الإيجابي للمستقبلات الهرمونية بسبب عدم وجود علاج معتمد. تم اعتماد استخدام العلاج الكيميائي التمهيدي بواسطة مركبات الأنثراسيكلين بالإضافة إلى عقار السيكلوفوسفاميد متبوعا بمركبات التاكسان لتحقيق الاستجابة الباثولوجية الكاملة. إضافة مركبات البلاتين إلى العلاج التمهيدي اصبحت تظهر نشاطا واعدا في مرضي سرطان الثدي الثلاثي السلبية.

هدف الدراسة: تهدف الدراسة إلى تقييم فعالية وسلامة إضافة مركبات البلاتين إلى العلاج الكيميائي التمهيدي في سرطان الثدي الثلاثي السلبية فيما يتعلق بالاستجابة الباثولوجية الكاملة للورم و المضاعفات الناتجة عن استخدام العلاج (المضاعفات الدموية وغير الدموية)

الطريقة المتبعة: دراسة ارتجاعية لسجلات 80 مريض من مرضي سرطان الثدي الثلاثي السلبية الذين خضعوا للعلاج الكيميائي التمهيدي إما باستخدام بروتوكول علاجي يحتوي علي مركبات البلاتين او خاليا منها.

النتائج: كان متوسط العمر48.5 ومن ضمن الحالات 50% في مرحلة مابعد انقطاع الطمث و55% من المرضي كان حجم الورم من الدرجة الثالثة او الرابعة. و45% كان لديهم ايجابية في العقد الليمفاوية الإبطية . تراوح حجم الورم من (12 :66ملم). بينما كان نطاق حجم العقد الليمفاوية من (صفر:40ملم). كانت معدلات الاستجابة الباثولوجية مواتية في المجموعة التي تلقت العلاج الكيميائي التمهيدي القائم علي مركبات البلاتين مع وجود دلالة احصائية (ب = 0.047) وقد كانت مضاعفات الدرجة الثالثة والرابعة في كلي المجموعتين متشابهة مع وجود فرق طفيف في بعض المضاعفات.

الاستنتاج: إضافة مركبات البلاتين إللي العلاج الكيميائي التمهيدي الخاص بمرضي سرطان الثدي الثلاثي السلبيه يؤدي إلي نتائج واعده في زياده عدد الاستجابات الباثولوجية الكاملة للاورام في هؤلاء المرضي مع وجود زياده طفيفة في بعض المضاعفات لذا يمكن وضعها في الاعتبار كعلاج فعال.