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Cisplatin Plus Gemcitabine Versus Paclitaxel Plus Gemcitabine as First-Line Therapy for Metastatic Triple Negative Breast Cancer

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ABSTRACT

Background: Although breast cancer management has generally improved, there is still a standing challenge represented by the triple-negative breast cancer whose recurrence is highly frequent, disease-free survival shortened, and the overall survival is extremely poor.

The Aim of Work: Compare between the total response rate of using gemcitabine/cisplatin versus paclitaxel/gemcitabine regimens to treat the metastatic triple-negative breast cancer cases.

Materials and Methods: A random clinical trial method carried out on patients with metastatic triple-negative breast cancer who attended to the Department of Oncology and Nuclear Medicine, Suez Canal University, in 2016/2017. A random assignment used to allocate patients who are qualified to: Group (A) to receive cisplatin /gemcitabine (cisplatin 75 mg/m² on day 1; gemcitabine 1000 mg/m² on days 1 and 8) or Group (B) to receive paclitaxel/gemcitabine (paclitaxel 175 mg/m² on day1; gemcitabine 1000 mg/m² on days 1 and 8) every 3 weeks for eight cycles at maximum or until the development of disease progression or the intolerable toxic effect.

Results: Cases of triple-negative breast cancer were 144 (20.9%) and those of metastatic triple-negative breast cancer were 110 (15.98%). Within a-12-month follow-up period, the total response rate of Group (A) was significantly higher than Group (B) (**69.1% versus 47.3%, respectively**). In addition, the median disease-free survival of Group (A) was significantly higher than that of the Group (B) (mean 7.18 versus 5.49 respectively).

Conclusion: Cisplatin/gemcitabine can be used alternatively, even a superior regimen to paclitaxel/gemcitabine, for patients with metastatic triple-negative breast cancer.

Keywords: chemotherapy, second line, metastatic cases.

INTRODUCTION

The pathological definition of triple-negative breast cancer is that it refers to estrogen receptor (ER)-negative, progesterone receptor (PR)- negative, and HER2-negative disease and its percentage ranges from 12 to 17% of all breast cancers[(1)] .

Although breast cancer management has generally improved, there is still a standing challenge represented by the triple-negative breast cancer whose recurrence is highly frequent, disease-free survival is greatly shortened, and the whole survival is extremely poor. However, other types of breast cancer have similar therapeutic approaches. Further, for the relapsed triple-negative breast cancer, the median distant disease-free survival ranges from 1 to 2 years. However, it is only 1 year for the metastatic triple-negative breast cancer [(2,3)].

The main systematic treatment for triple negative breast cancer is the cytotoxic chemotherapy. Particularly, when the DNA repair agents, PARP inhibitors, EGFR inhibitors, antiangiogenic agents, or checkpoint kinase 1 (Chk1) inhibitors (with or without chemotherapy) are used as targeted approaches, they do not improve the triple-negative breast cancer outcomes substantially [(4,5)].

There is a general overlap between the molecular signature of triple-negative breast cancer and the basal-like breast cancer where their concordance ranges from 70 to 90 %[(6)].

Moreover, the mutations of BRCA, ***(breast cancer gene)*** which are prevalently reported in unselected patients suffering from triple-negative breast cancer, are 11.2% higher than those of wider population suffering from breast cancer[(7)]. The characteristics of breast cancer which is associated with BRCA or the sporadic triple-negative or basal-like breast cancer have a consistency with the abnormal DNA repair and genome-wide instability. In turn, this supports using the DNA-damaging compounds such as platinum [(8)].

In the past years, a lot of researchers have paid attention to examining the platinum-based therapy in the setting of neoadjuvant or metastatic triple-negative breast cancer[(8,9)]. Two random phase 2 studies, GeparSixto and CALGB 40603, indicated that when carboplatin is added to the neoadjuvant therapy of triple-negative breast cancer, there were an increase in the number of patients displaying a complete pathological response [(10, 11)].

Further, when the cisplatin is compared to the carboplatin, it achieves a higher efficacy in neoadjuvant setting of locally advanced triple-negative breast cancer, the number of patients displaying a complete pathological response increases, and the overall survival improves significantly [(12)].

In addition, cisplatin has achieved more complete and partial response than carboplatin in the metastatic setting[(13)]. Moreover, a phase-2 study carried out in

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2010 on gemcitabine and cisplatin showed that they are used as a first-line combined therapy of patients suffering from metastatic triple-negative breast cancer [14].

As a result, for a better control of triple-negative breast cancer in the neoadjuvant and metastatic settings using the cisplatin, the preclinical evidence for the effect of synergy between cisplatin and gemcitabine regimen when they are used as a first-line therapy of metastatic triple-negative breast cancer will not be stronger nor weaker than those of the standard regimen of paclitaxel plus gemcitabine [15,16,17].

PATIENTS AND METHODS

A random assignment is used to allocate patients who are qualified to receive either cisplatin plus gemcitabine or paclitaxel plus gemcitabine.

The study was approved by the Ethics Board of Suez Canal University University.

- Patients were assigned either to:

1. Group (A): cisplatin plus gemcitabine (cisplatin 75 mg/m² on day 1; gemcitabine 1000 mg/m² on days 1 and 8). Or
2. Group (B): paclitaxel plus gemcitabine (paclitaxel 175 mg/m² on day1; gemcitabine 1000 mg/m² on days 1 and 8) intravenously every 3 weeks for eight cycles at maximum or until the development of disease progress or the intolerable toxic effect.

- The key criteria for including patients are: metastatic triple-negative breast cancer, no chemotherapy for metastatic disease has been used previously, at least one extra cranial lesion which can be measured by MRI or CT in accordance with the response evaluation criteria in solid tumors, and the performance status of 0-1-2 of the Eastern Cooperative Oncology Group.
- The key criteria of excluding patients are: patients who were not triple-negative breast cancer, the potential of giving birth to a child with no willingness to use the adequate contraception, symptomatic or unstable CNS metastases, life expectancy not to be more than three months.
- The median period of follow-up is determined to be 1 year.

RESULTS

Triple negative breast cancer cases were **144 case (20.9%),** while metastatic triple negative breast cancer cases were **110 (15.98%)** presented to Clinical Oncology and Nuclear Medicine Department Suez Canal University.

* Most patients were above the age of 40 years**. (72.7%)** were more than or equal 40 years in group (A) receiving gemcitabine cisplatin , while **(83.6%)** were in group (B) receiving paclitaxel gemcitabine.Only **27.3%** of the patients were under the age of 40 years in group A and **16.4%** in group B. Mean age was 46.

*Regarding residence, **86 patients (78.18%)** of the studied patients were from Ismailia. **50 (45.45%)** of the studied patients were housewives, while **34 (31%)** patients were employee and 26 (23.55 %) were retired.

***(71%) of patients** were ECOG performance status 1, while **(29%)** were ECOG performance status 0.

***According to marital status, 97 (88.2%)** patients of the studied patients were **married**, **93 (84.54%)** patients had got married **between 20 and 30 years old**.

***According to usage of oral contraceptive pills, 50 (45.45%)** patients used oral contraceptive pills while **60 (54.54%)** patients did not use the pills.

***Regarding menopausal status, 45 (41%)** patients among both groups were premenopausal while **65 (59%)** patients were post-menopausal.

* **8** patients **(7.27%)** were smokers while **102** patients **(92.73%)** were non-smoker.

***** **109 (99.1%)** patients had their menarche after the age of 11 years.

* **101 (92%)** patients of the studied patients were not having family history of breast cancer, while only **9 (8%)** patients were having **positive family history**.

***Regarding pathological picture, 62 patients (56.4%)** were having invasive ductal carcinoma , **13 patients (11.8%)** were invasive lobular carcinoma , **13 patients (11.8%)** were having mixed ductal and lobular carcinoma and **22 patients (20%)** had other types.

No patients were T1, 68 patients (62%) were T2, 32 patients (29.09%) were T3 and 10 patients (8.91) were T4.

No patients were grade 1 at presentation, 56 patients (50.9%) were grade 2 and 56 patients (49.1%) were grade 3.

43 patients (39.09%) were N0, 60 patients (54.55%) were N1, 17 patients (6.36%) were N2 and no patients were N3.

27 patients (24.55%) were **stage 2A** at the time of presentation, **43 patients** (39.09%) were **stage 2B , 30 patients** (27.27%) were **stage 3A** and **10 patients** (9.09%) were **stage 3B.**

* According to the **first line chemotherapy received, 61 patients (55.45%)** of the studied sample received anthracycline only as a first line chemotherapy, **12 patients (10.9%)** received taxenes alone as a first line and **37 patients (33.65%)** received both anthracyline and taxenes as a first line chemotherapy.

*According to received metronomic chemotherapy, 24 patients (21.8%) received capcitabine (Xeloda) as a metronomic chemotherapy after receiving first line

chemotherapy and before the development of metastasis.

*__According to time between surgery and recurrence,__ 6.36% of the study group developed Recurrence less than or equal to 6 months from Surgery. 29.1% developed Recurrence from 6 months to less than 1 year from surgery. 47.27% developed Recurrence from 1 to 2 years from surgery. 8.18% developed Recurrence from 2 to 5 years from surgery. 9.09% developed Recurrence more than 5 years from surgery.

*__46 patients (41.81%)__ of the studied patients developed one site of metastasis, __28 patients (25.45%)__ developed 2 sites of metastasis and __36 patients (32.74%)__ developed more than or equal 3 sites of metastasis.

*__According to metastatic sites, 57 patients (51.8%)__ developed lung metastasis, __31 patients (28%)__ developed liver metastasis, __6 patients (5.5%)__ developed brain metastasis, __24 patients (22%)__ developed bone metastasis, __7 patients (6.4%)__ developed metastasis in contralateral breast, __61 patients (55.45%)__ developed metastasis in lymph nodes, __10 patients (9.1%)__ developed metastasis in pleura and __17 patients (15.45%)__ developed metastasis in chest wall and skin.

*__55__ patients were randomized to have __(4) cycles__ of __(Gemcitabine, Cisplatin)__ and __overall tumor response__ was assessed after that, and revealed that:

* __(5)__ Patients (9.1%) had __complete tumor response (CR), both clinically and radiological__.

* __(33)__ Patients (60%) had __partial tumor response (PR)__, both clinical and radiological.

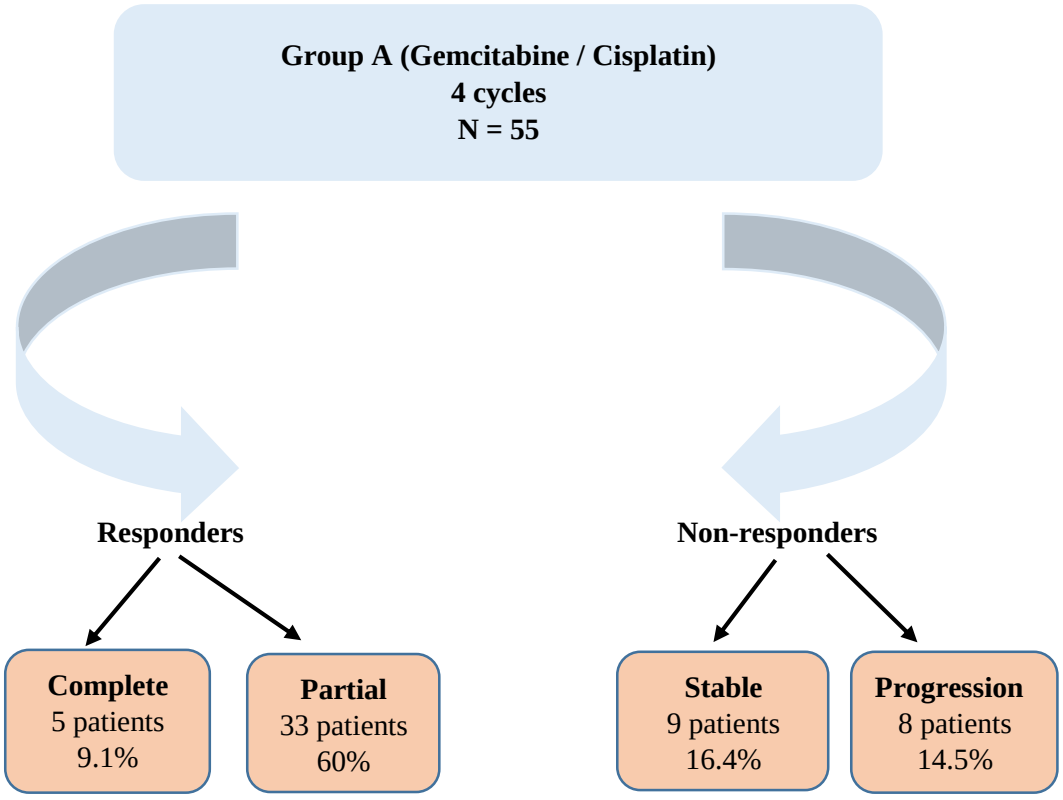
* Those patients received __(2) additional cycles__ of the same regimen.

__The Overall tumor response for this group was 69.1%__

- __(9)__ Patients (16.4%) had __stable disease course, both clinically and radiological__.
- __(8)__ Patients (14.5%) had __progression,__ both clinical and radiological.

* __Non Responders__ were 17 patients __(30.9%)__ to initial line of treatment (__4 cycles of gemcitabine, cisplatin__) were __switched__ to having __another regimen.__

Diagram (1) Tumor response:



__The Overall tumor response for this group was 69.1%.__

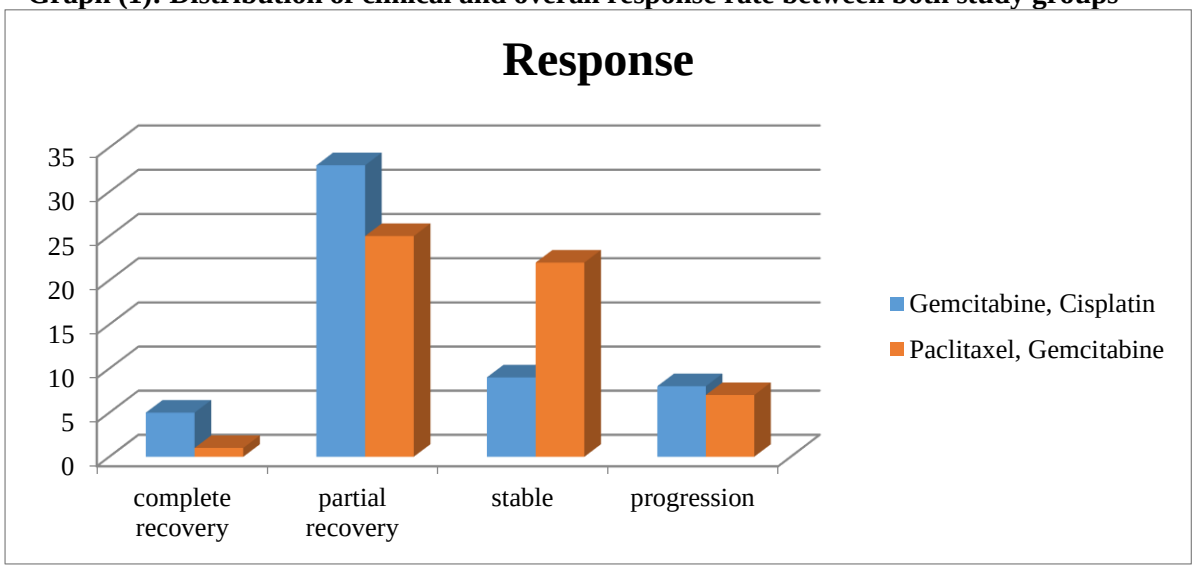
*__55__ patients were randomized to have __(4) cycles__ of __(paclitaxel, gemcitabine)__ and __overall tumor response__ was assessed after that, and revealed that:

- __(1)__ Patients (1.8 %) had __complete tumor response (CR), both clinically and radiological__.
- __(25)__ Patients (45.5 %) had __partial tumor response (PR)__, both clinical and radiological.

Those patients received __(2) additional cycles__ of the same regimen.

__The overall tumor response for this group was 47.3 %__

*** Graph (1): Distribution of clinical and overall response rate between both study groups**

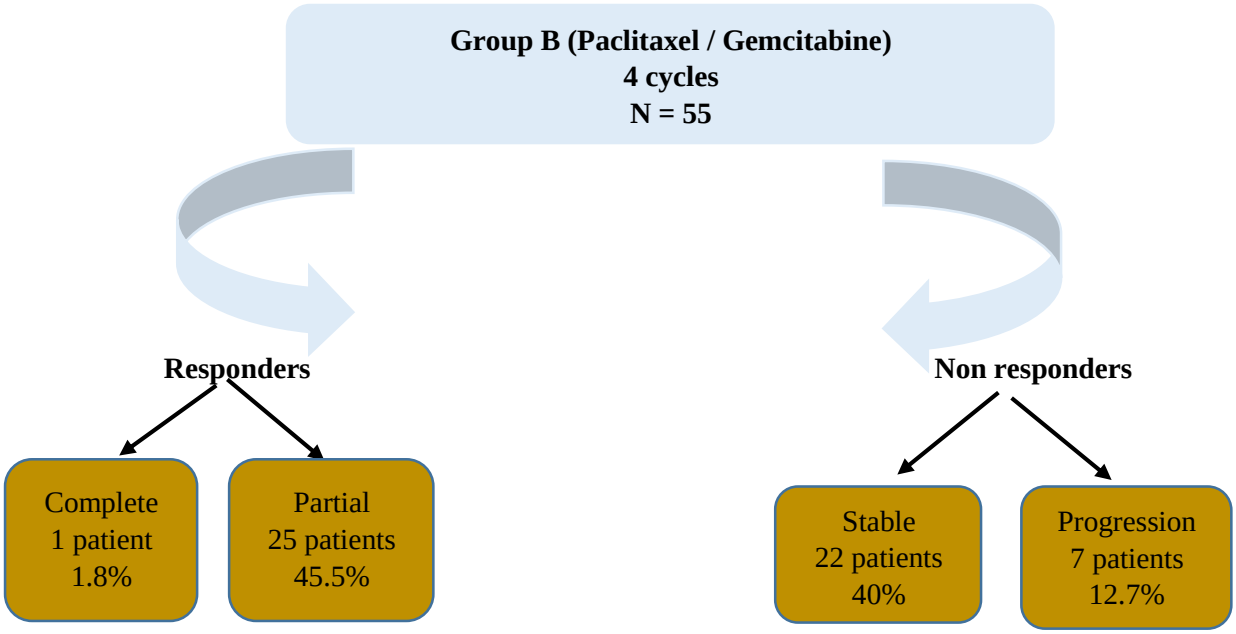


P value were significant. ***(P value of clinical and overall response rate between both study groups)***

- **(22)** Patients (40%) had **Stable disease course, both clinically and radiological**.
- **(7)** Patients (12.7%) had **progression,** both clinical and radiological.

* **Non-responders** were **(52.7 %)** patients to initial line of treatment (**4 cycles of paclitaxel, gemcitabine**) were **switched** to having **another regimen**.

Diagram 2: Tumor response:



The Overall tumor response for this group was 47.3 %

P value were 0.026* ***(P value of overall tumor response rate between both study groups)***

* According to progression free survival, median progression free survival for gemcitabine cisplatin arm was 8 months **(Mean 7.18)**, while median progression free survival for paclitaxel gemcitabine arm was 6 months **(Mean 5.49).**

Median progression free survival (DFS) for the **(gemcitabine, cisplatin)** arm was **significantly higher** than **median progression free survival (DFS)** for the **(paclitaxel gemcitabine).**

*** Graph (2): Progression free survival among both study groups:**

		Gemcitabine Cisplatin (N=55)	Paclitaxel Gemcitabine (N=55)	P-value
Progression free survival (PFS) In months	**Mean ± SD**	7.18 ± 3.209	5.49 ± 2.292	0.002*
	Median	8.00	6.00	
	Min – Max	0-10	0-8	

* Statistically significant difference between both groups (P value < 0.05)

Hematological side Effects more commonly happened with the patients who received **(paclitaxel + gemcitabine)** in comparison to those received **(gemcitabine + cisplatin)**.

The most common non-hematological side effects for those who had **(gemcitabine + cisplatin)** were **nausea and vomiting** in **42 patients (76.4 %)** with significant statistical difference versus group B (paclitaxel + **gemcitabine**) (77 patients).

The most common non hematological side effects for those who had **(paclitaxel + gemcitabine)** were * **Musculoskeletal pain** in **21**patients (38.2%)

* **Neuropathy** in **29** patients (52.7%)
* **Fatigue** in **17** patients (30.9%)
* **Alopecia** in **10** patients (18.2%)

*The most common laboratory finding for those receiving **gemcitabine cisplatin** was **hypomagnesaemia** in **13 patients (23.6%)**.

DISCUSSION

The characteristics of triple-negative breast cancers (TNBC) are the lack of estrogen receptor (ER), the lack of progesterone receptor (PR), and the lack of over-express human epidermal growth factor receptor 2 (HER2). Such types of cancers normally have relationships with poor prognosis because of the aggressive tumor phenotype(s), the partial response to chemotherapy, and the lack of targeted therapies, which are clinically developed. [18,19]

In terms of the response of tumor to second-line chemotherapy, the results of **Koshy *et al* .** study showed an improvement in the outcome for patients with metastatic triple-negative breast cancer compared to patients without metastatic triple-negative breast cancer when they are treated with the combination chemotherapy of cisplatin and gemcitabine. In addition, the cisplatin and gemcitabine combination compared to paclitaxel and gemcitabine within the period of 3.7 months made a difference in the disease-free survival between the two groups under study. [20]

Chew et al. found similar findings in a phase II trial study carried out using the cisplatin and gemcitabine to treat patients who experienced minimal prior therapy. The response rate of patients with ER/PR negative was 43% compared to 8% of patients with ER/PR positive (the status of HER2 was not determined) but the results showed no difference in response for patients who were heavily treated with chemotherapy. [21]

On the other hand, the findings of **Maisano *et al.* indicated that the combination of** carboplatin and gemcitabine (CG) is considered the active and reasonable option for the treatment of unselected patients with anthracycline/taxane pretreated metastatic breast cancer [22]. In addition, **Erten *et al.*** found that the combination of cisplatin and gemcitabine regimen is well-tolerated option for the treatment of patients with brain metastasis resulting from breast cancer. Further, they showed the results supporting the use of this regimen for the treatment of the triple-negative subtype are the longer PFS and the higher response rate. [23]

Hu *et al.* carried out an open-label, randomized, 3 phase, hybrid-designed trial study on patients aged from 18 to 70 years old in 12 hospitals in China. The patients were not treated before and it was confirmed histologically that they suffered from metastatic triple-negative breast cancer and the status of ECOG performance was 0-1. The study assigned patients randomly (1:1) in order to receive either the combination of cisplatin and gemcitabine (cisplatin 75 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8) or the combination of paclitaxel and gemcitabine (paclitaxel 175 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8) through the veins every 3 weeks for eight cycles at maximum. Then, they found that the combination of cisplatin and gemcitabine can be used alternatively as the preferred first-line tool of chemotherapy for patients suffering from metastatic triple-negative breast cancer.[24]

Based on the above-mentioned findings, the current study showed that the total response rate for gemcitabine cisplatin regimen was 69.1% and 47.3% for paclitaxel gemcitabine regimen. Furthermore, the gemcitabine cisplatin arm has resulted in a median progression of free survival of 8 months (the mean is 7.18) and it was 6 months for the paclitaxel gemcitabine (the mean is 5.49).

CONCLUSION

The current study showed that, compared with the more established standard regimen of paclitaxel plus

gemcitabine, cisplatin plus gemcitabine regimen is not inferior and could even be superior in term of overall response and disease-free survival. In addition, the results of the study showed that the two regimens are well-tolerated with the different profiles of toxicity. The results suggested that the combination of cisplatin and gemcitabine can be used alternatively as the preferred first-line option for the chemotherapy of patients suffering from the metastatic triple-negative breast cancer.

As a result, we concluded that the cisplatin plus gemcitabine can be considered as an alternative or the preferred first-line chemotherapy for patients suffering from the metastatic triple-negative breast cancer.

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