Use of Vinorelbine/Cisplatin regimen Versus Docetaxel/Gemcitabine regimen in Operable Locally Advanced Breast Cancer Patients

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Abstract: Background: Locally advanced breast cancer continues to be a common breast cancer presentation worldwide and to be a significant problem in Egypt. The National Cancer Institute of Cairo data showed breast cancer stages III and IV to be around 80 - 90%. **Aim of Work:** To compare the Response Rate & Toxicity of using Vinorelbine/Cisplatin regimen versus Docetaxel/Gemcitabine regimen as a tool of treatment in Operable Locally Advanced Breast Cancer patients. **Patients & Methods:** This was a randomized clinical trial study that was conducted upon clinically, pathologically & radiologically proved patients with Locally Advanced Breast Cancer attending Clinical Oncology and Nuclear Medicine Department of Suez Canal University during 2013 & 2014 at Ismailia. Patients recruited for the study were divided into two main groups as follows: **Group (1):** included patients who received 4 cycles of (Vinorelbine, Cisplatin) regimen. **Group (2):** included patients who received 4 cycles of (Docetaxel, Gemcitabine) regimen. **Results:** (Vinorelbine, Cisplatin) regimen was more effective and well-tolerated than (Docetaxel, Gemcitabine) regimen in patients with Locally Advanced Breast Cancer with Overall Response Rate: (84.44%, 53.33%) respectively. Disease Free Survival & Overall Survival for those who had pathological complete tumor & nodal response after receiving either (Vinorelbine, Cisplatin) or (Docetaxel, Gemcitabine) regimens during 19 months of follow-up were (100%) with significant statistical difference. **Conclusion:** Pathological complete remission to neoadjuvant chemotherapy has been consistently associated with improved disease free survival and overall survival.

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1. Introduction & Rationale

Locally advanced breast cancer (LABC) continues to be a common breast cancer presentation worldwide and to be a significant problem in Egypt and the United States that National Cancer Institute of Cairo data showed breast cancer stages III and IV to be around 80 - 90% [(1)]. LABC generally is defined by bulky primary chest wall tumors and/or extensive adenopathy. This includes patients with T3 (> 5 cm) or T4 tumors (chest wall fixation or skin ulceration and/or satellitosis) and N2/N3 disease (matted axillary and/or internal mammary metastases) [(2)]. Recent studies demonstrate that prolonged survival can be achieved in patients with metastatic disease limited to the supraclavicular nodes after appropriate multimodality breast cancer treatment [(2), (3)]. As a result, the sixth edition of the American Joint Committee on Cancer (AJCC) staging system now includes isolated supraclavicular metastases in the stage III/LABC disease category [(4)]. According to the American College of Surgeons National Cancer Data Base, approximately 6%of breast cancers in the United States present as stage III breast cancer disease [(5)]. Five-year survival for stage III breast cancer is approximately 50%, compared with 87% for stage I.

The extent to which LABC represents neglect and delayed diagnosis versus aggressive tumor biology is unclear. Data from the Surveillance, Epidemiology, and End Results (SEER) program reveal that the proportion of LABC is higher among women of African, Hispanic, and Native American descent compared with white and Asian Americans, contributing to increased mortality in these populations. These disparities reflect socioeconomic and health care access inequalities, but parallel variations in the incidence of breast cancer based on country of origin also suggest the existence of environmental and genetic factors [(5)].

Surgeons historically have been at the forefront of investigating LABC treatment. Haagensen and Stout [(6)] at Columbia University provided early data regarding the dismal results of radical mastectomy alone as treatment for LABC over 60 years ago, reporting 5-year local recurrence and survival rates of 46% and 6%, respectively. This experience led to the definition of inoperable LABC when patients presented with extensive breast skin edema or

satellitosis, intercostal/parasternal nodules, arm edema, supraclavicular metastases, or inflammatory breast cancer. Grave local signs of LABC were poor prognostic features, but not contraindications to resection. These included ulceration, limited skin edema, fixation to the pectoralis muscle, and bulky axillary adenopathy. Therapeutic doses of chest wall radiation were similarly inadequate in controlling LABC. Studies from the 1970s and 1980s by the Joint Center for Radiation Therapy, Guy's Hospital, and the Mallincrodt Institute of Radiology all revealed excessively high failure rates, with 5-year local recurrence rates ranging from 46% to 72%, and survival rates of 16% to 30% [7], [8], [9]. Combined treatment with radiation and surgery was also attempted in this era [10], [11], [12], but yielded no significant improvement in disease control.

Preoperative chemotherapy protocols (also known as neoadjuvant or induction chemotherapy) revolutionized LABC care and this approach is now standard for patients with bulky breast and/or axillary disease. Early concerns regarding this approach were based on the potentially negative effects of preoperative chemotherapy on: surgical complication rates, the prognostic value of the axillary staging, and overall survival after delayed surgery. Clinical investigations reported during the 1980s and 1990s alleviated these concerns [13]. Currently, optimal control is achieved with preoperative chemotherapy followed by surgery and radiation. Preoperative versus postoperative chemotherapy have been directly compared in women with LABC and also in women with early stage breast cancer. These prospective clinical trials have demonstrated overall survival equivalence for the two sequences, confirming the oncologic safety of the neoadjuvant approach [13], [14], [15], [16], [17], [18], [19], [20]. As patients with LABC benefit from the tumor downstaging and improved resectability that can be achieved with neoadjuvant chemotherapy, this sequence has become the preferred approach for patients with bulky, locally advanced disease at time of diagnosis [13], [14], [15], [16], [17], [18], [19], [20].

Establishing a tissue diagnosis is the initial priority on presentation of LABC. In many patients, core biopsy of the tumor, either freehand or under ultrasound guidance is diagnostic. Core needle is preferred over fine needle aspiration, as cytology is insufficient to confirm invasion. Multiple cores should be extracted to confirm invasive cancer and to evaluate hormone receptor status and HER2/neu expression. This is critical, because palpable ductal carcinoma in situ (DCIS) does exist, and induction chemotherapy is inappropriate for DCIS, even with microinvasion [21]. After a tissue diagnosis is established, LABC patients should undergo multidisciplinary review before treatment. The multidisciplinary team should include surgical, medical and radiation oncologists, pathologists, radiologists, and plastic surgeons, creating a unified treatment proposal and thereby minimizing the possibility that inconsistent messages will be delivered to the patient by the various specialists involved with the management plan. A baseline bone scan, and chest, abdominal, and pelvic CT scans are recommended for detection of metastatic disease. Directed radiographs to sites of new bone pain, or a head CT scan for new neurologic symptoms are also recommended in selected cases [22]. Patients receiving preoperative chemotherapy should be reassessed after one or two cycles and again at the completion of therapy to document response and explore surgical options. Imaging may be repeated at the interim evaluation. If minimal or no response is observed after the initial cycles a decision should be made to either proceed with surgery or to cross over to a different systemic therapy. Salvage surgery allows for a full pathologic evaluation and facilitate decisions on adjuvant therapy. If an alternative regimen is selected, reassessment after two cycles of the crossover treatment is necessary. Follow-up imaging is essential after complete delivery of neoadjuvant therapy for final preoperative surgical planning [22].

Currently, doxorubicin-based chemotherapy is the most widely-studied induction regimen, and it results in at least 50% tumor shrinkage in more than 75% of cases. The NSABP B-27 protocol randomized patients with resectable breast cancer to one of three neoadjuvant treatment arms: (1) doxorubicin and Cytoxan alone; (2) doxorubicin, Cytoxan, and docetaxel; or (3) preoperative doxorubicin and Cytoxan followed by postoperative docetaxel. Preliminary data [23] revealed a pCR rate of 26% associated with the addition of docetaxel to the preoperative regimen. Also, the University of Texas M.D. Anderson Cancer Center [24] has reported a pCR rate of nearly 30% in patients treated with preoperative doxorubicin, Cytoxan,5-fluorouracil, and weekly Taxol.

Neoadjuvant endocrine therapy for estrogen receptor-positive LABC also carries great promise. Three-to-four months of therapy are preferred for an adequate response assessment, and preliminary studies suggest that aromatase inhibitors such as letrozole are more effective than Tamoxifen [25], [26]. Other neoadjuvant regimens had been evaluated include trastuzumab, Navelbine, capecitabine, and gemcitabine.

A clinical phase II study of **Cisplatinum** and **Vinorelbine (PVn)** in advanced breast carcinoma (ABC) was done by Shamseddine A et al and was published in the American Journal of Clinical

Oncology at 2005 and stated that PVn was effective as first line treatment of advanced breast cancer with overall response rate of 64% in metastatic breast cancer and 92.3% in locally advanced breast cancer, and had acceptable toxicity [27].

Among several different promising new cytotoxic agents currently undergoing clinical evaluation in Advanced Breast Cancer (ABC) [28] is the novel nucleoside analogue of deoxycytidine Gemcitabine. It possesses a broad range of activity against various solid tumors, and is characterized by a favorable toxicity profile [29], [30], [31], [32], [33], [34]. Gemcitabine whether used as single agent or in combination regimens, it showed an objective response rate of 25–46% in ABC patients, depending on whether this drug was used as first- or second-line treatment [35], [36], [37].

Docetaxel is another anticancer agent of the taxanes class that has also been demonstrated to be highly effective when given as a single agent or when combined with other drugs [38], [39]. Docetaxel promotes tubulin assembly into microtubules, stabilizes microtubules, and inhibits depolymerization to free tubulin [39]. Recently, favorable results have been reported when these two drugs were used in combination for the treatment of advanced non-small cell lung cancer [40], [41] and in two Phase II trials of chemorefractory ABC, yielding an objective response rate as high as 54% [42], [43].

2. Patients & Methods

It is a randomized clinical trial study that was conducted upon clinically, pathologically & radiologically proved patients to have Locally Advanced Breast Cancer attending Clinical Oncology and Nuclear Medicine Department of Suez Canal University during 2013 & 2014 at Ismailia. Patients recruited for the study were divided into two main groups as follows: **Group (1):** included patients who received **4 cycles** of (Vinorelbine, Cisplatin) regimen: **Vinorelbine** 30 mg/m^2 on days 1 and 8 / **Cisplatin** 75 mg/m^2 on day 1 regimen of a 21 day cycle. **Group (2):** included patients who received **4 cycles** of (Docetaxel, Gemcitabine) regimen: **Docetaxel** 75 mg/m^2 on day 1/ **Gemcitabine** 1 gm/m^2 on day 1 and 8 regimen of 21 day cycle.

Inclusion criteria: Patients were selected when they fulfill the following criteria: Patients aged more than 18 years and less than 80, clinically, pathologically & radiologically proved patients with Operable Locally Advanced Breast Cancer, Study participants will be counseled, and an informed written consent will be obtained.

Exclusion criteria: Patients with performance status more than II, Patients with (double pathology) another cancer in the body, Patients with contraindication for chemotherapy as pancytopenia, impaired liver function and renal function, Refusal of participation in the study or failure to obtain an informed consent. Doing Physical & Clinical examination of the affected, the contralateral breasts & the regional lymphatics, Complete Blood Count, Liver and Renal function tests, Chest X-ray and Pelvi-Abdominal Ultrasonography were done after finishing the course of treatment which is **(4) cycles** of one the pre specified regimens of chemotherapy comparing the results with the previous one before starting the treatment. Once **clinical complete tumor response (cCR)** had happened after **(4) cycles** of any of the pre specified regimens of chemotherapy, the patient was referred to do surgery. If there was **clinical partial tumor response (cPR)** after having **(4) cycles** of one the pre specified regimens of chemotherapy, the patient had **(2) more additional cycles** of chemotherapy of the same regimen given before. If there was **no response** after having **(4) cycles** of any of the pre specified regimens of chemotherapy, the patient was switched to have the other regimen of chemotherapy for another **(4) cycles** then the tumor was reassessed clinically. The study aims to make the locally advanced breast cancer patients reach surgery, so that all the patients who reached clinical complete response were referred to do surgery and all the patients who reached clinical partial tumor response & clinical stable disease also were referred to do surgery.

3. Results

Diagram (1) shows that the Clinical Complete Tumor Response (cCR) for those who had received (Vinorelbine, Cisplatin) was superior to those who had received (Docetaxel, Gemcitabine): (42.22% & 17.77% respectively). Clinical Partial Tumor Response (cPR) for those who had received (Vinorelbine, Cisplatin) was superior to those who had received (Docetaxel, Gemcitabine): (42.22% & 35.55% respectively).

Overall Response Rate (OR) for those who had received (Vinorelbine, Cisplatin) was superior to those who had received (Docetaxel, Gemcitabine): (84.44% & 53.33% respectively) with significant statistical difference.

Diagram (2) shows that the **Clinical Complete Nodal Response (cCR)** for those who had **+ve clinical lymphadenopathy** at entry & had received **(Docetaxel, Gemcitabine)** was superior to those who had received **(Vinorelbine, Cisplatin)**: (**76.66%** & **63.33%** respectively) with significant statistical difference.

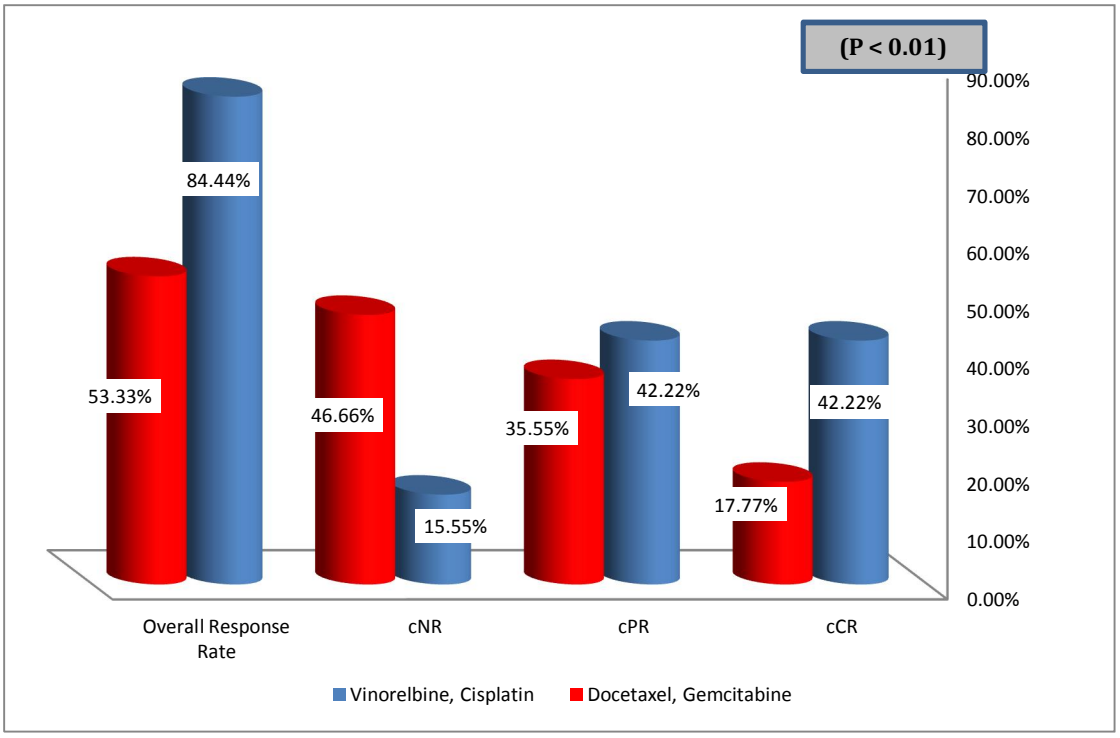
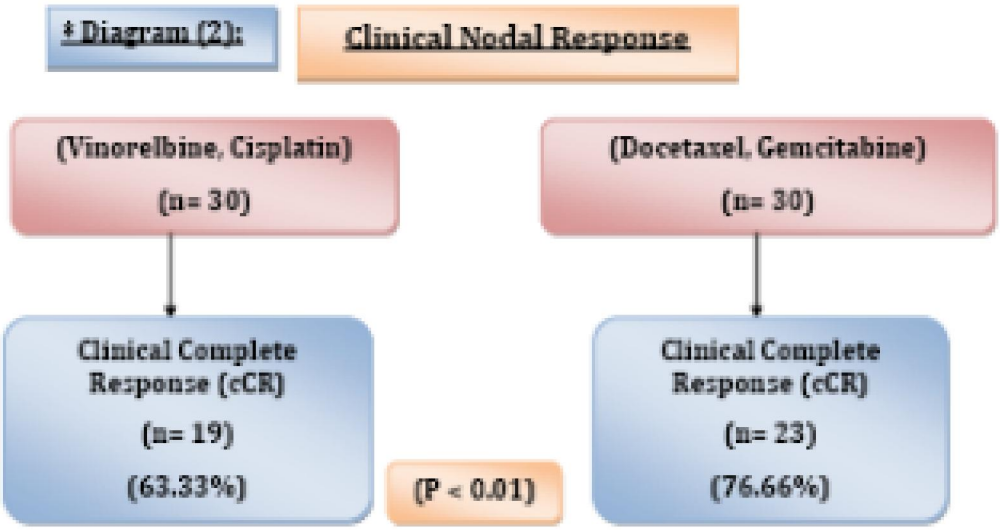


Diagram (1): Distribution of Clinical & Overall Response rate among both study groups:



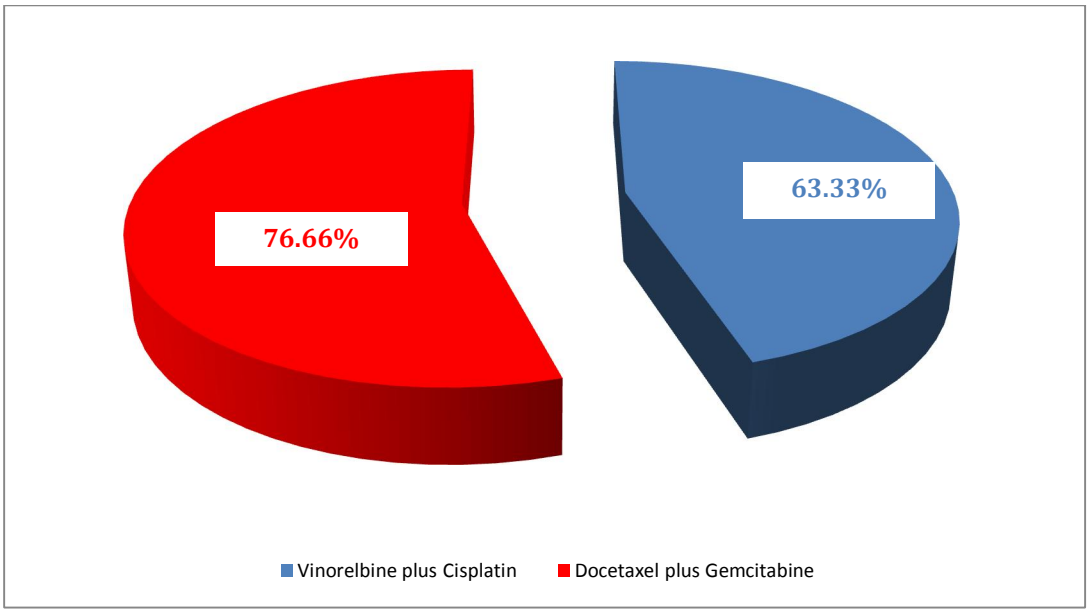


Diagram (2)

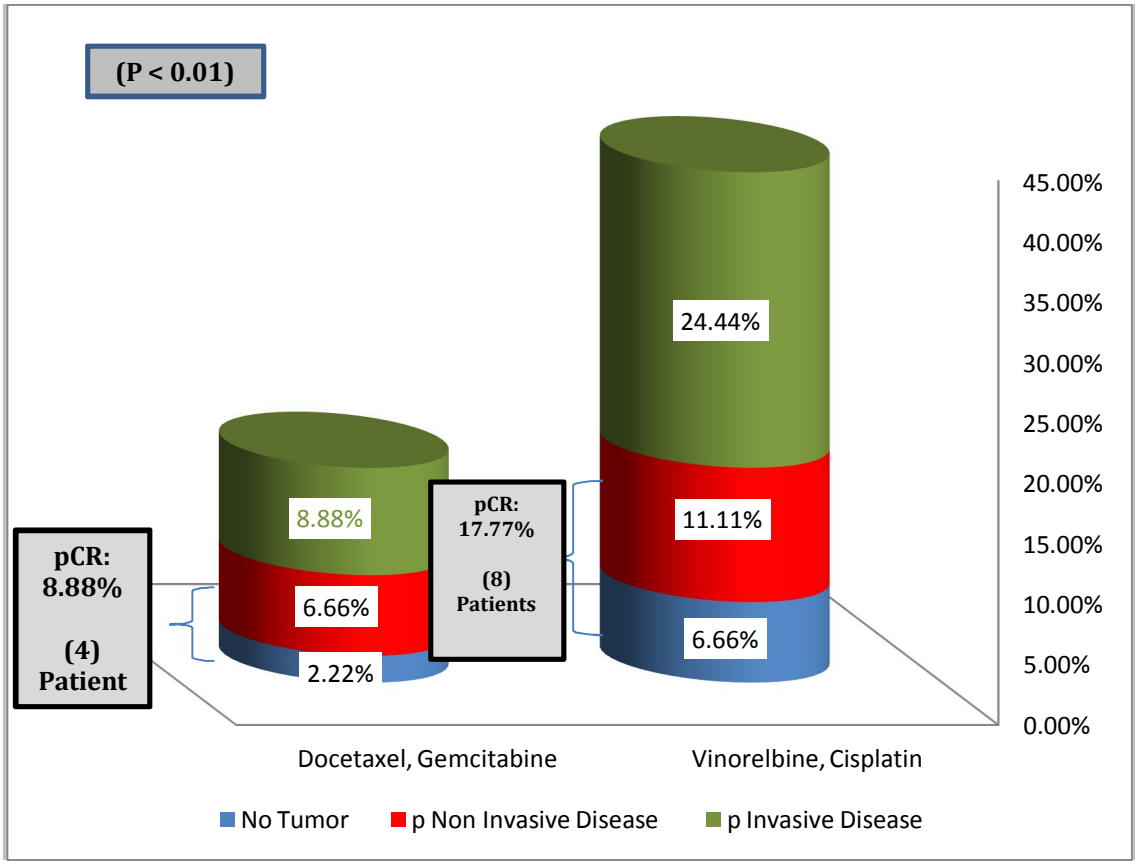


Diagram (3): Distribution of Pathological Tumor Response rate for those who had Clinical Complete Tumor Response (cCR) among both study groups:

Diagram (3) shows that the **Pathological Complete Tumor Response (pCR) (No Residual Tumor + Pathologic Non Invasive Disease)** after doing Modified Radical Mastectomy for those who had received **(Vinorelbine, Cisplatin)** was superior to those who had received **(Docetaxel, Gemcitabine)**: (**17.77%** & **8.88%** respectively) with significant statistical difference.

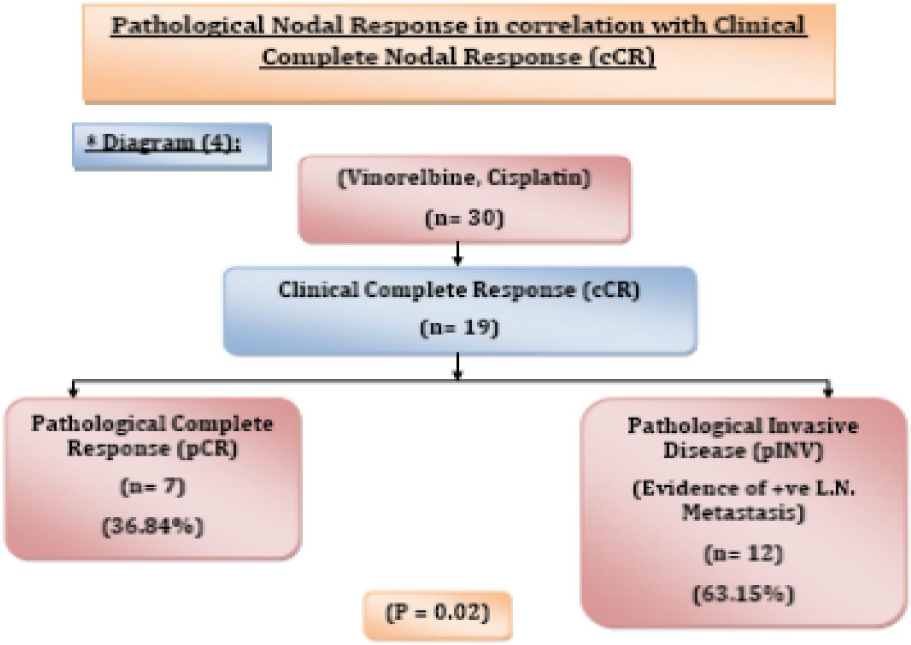


Diagram (4)

Diagram (4) shows that the **Pathological Complete Nodal Response (pCR)** for those who had **Clinical Complete Nodal Response** after having **(Vinorelbine, Cisplatin)** regimen was **36.84%** with significant statistical difference.

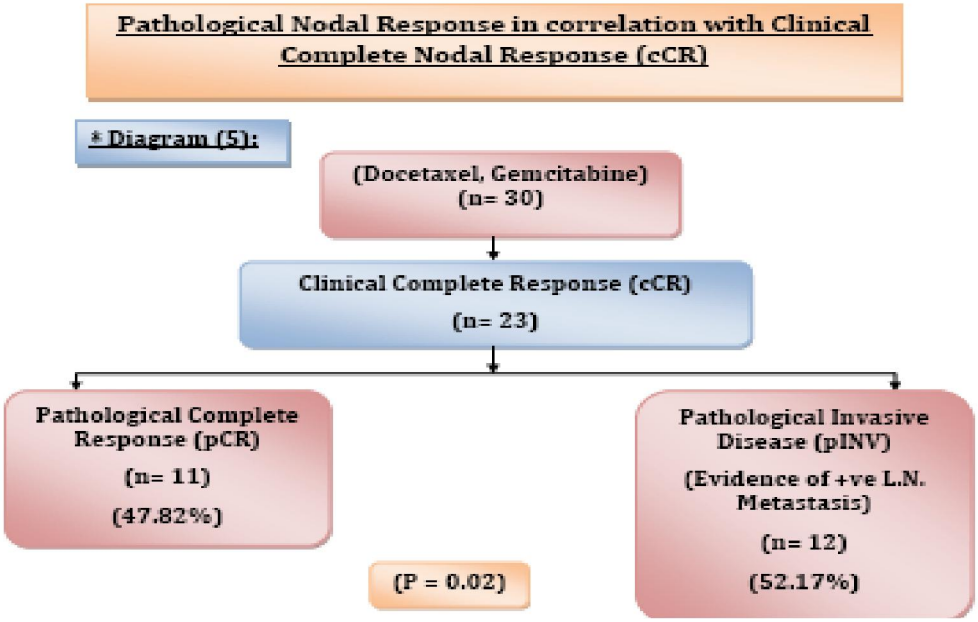


Diagram (5): **Pathological Complete Nodal Response (pCR)** for those who had **Clinical Complete Nodal Response** after having **(Docetaxel, Gemcitabine)** regimen was **47.82%** with significant statistical difference.

* So that, totally, 18 (20%) patients were having no evidence of pathological L.N. metastasis after neo-adjuvant chemotherapy regimens, but 72 (80%) patients were having +ve evidence of L.N. metastasis.

Table (1): Toxicity Profile among both study groups:

			Vinorelbine, Cisplatin (n=66)		Docetaxel, Gemcitabine (n=52)		P-value
Hematological Side effects	**Anemia**	**Grade 2**	10	15.5%	**21**	**40.38%**	**0.01***
		Grade 3	2	3.03%	1	1.91%	
	Neutropenia	**Grade 2**	7	10.06%	**20**	**38.4%**	**0.05***
		Grade 3	2	3.03%	**11**	**21.1%**	
	Low platelet count	**Grade 2**	0	0%	3	5.7%	**0.2 (NS)**
Non Hematological Side effects	**Nausea & vomiting**	**Grade 2**	**21**	**31.8%**	5	9.6%	**0.04***
		Grade 3	1	1.5%	0	0%	
	Neuropathy	**Grade 1**	**20**	**30.3%**	**20**	**38.4%**	**0.1 (NS)**
		Grade 2	4	6%	**11**	**21.1%**	
	Fatigue	**Grade 1**	11	16.6%	**61**	**30.7%**	**0.6 (NS)**
		Grade 2	1	1.5%	3	5.7%	
	Stomatitis	**Grade 2**	15	22.7%	**17**	**32.6%**	**0.3 (NS)**
		Grade 3	1	1.5%	4	7.6%	
	Elevated Serum Creatinine	**Grade 2**	2	3.03%	1	1.9%	**0.8 (NS)**
	Infusion related reactions	**Grade 2**	2	3.03%	5	9.6%	**0.01***
	Thrombophlebitis	**Grade 2**	**34**	**51.5%**	1	1.9%	**0.01***
		Grade 3	4	6%	0	0%	

***:** statistically significant difference. **N.S:** no statistically significant difference

Table (1) shows that **Haematological Side Effects** more commonly happened with the patients who received **(Docetaxel, Gemcitabine)** in comparison to those received **(Vinorelbine, Cisplatin)**. The most significant Haematological Side Effects occurred for the patients who had received **(Docetaxel, Gemcitabine)**: **21(40.38%)** patients had **Grade 2 Anemia**, **20 (38.4%)** patients had **Grade 2 Neutropenia**, and **11 (21.1%)** patients had **Grade 3 Neutropenia** with significant statistical difference.

The most common Non Haematological Side Effects happened for those who had **(Vinorelbine, Cisplatin)** were: (**Grade 2 Nausea & vomiting** in **21 (31.8%)** patients, **Grade 1 Neuropathy** in **20 (30.3%)** patients and **Grade 2 Thrombophlebitis** in **34 (51.5%)** patients) with significant statistical difference.

The most common Non Haematological Side Effects happened for those who had **(Docetaxel, Gemcitabine)** were: (**Grade 1 Neuropathy** in **20 (38.4%)** patients, **Grade 2 Neuropathy** in **11 (21.1%)** patients, **Grade 1 Fatigue** in **16 (30.7%)** patients and **Grade 2 Stomatitis** in **17 (32.6%)** patients).

* Overall Survival (OS) during 19 months of follow-up for Responders in general at both study groups was 100% with good performance status with significant statistical difference (P = 0.02).

Table (2): Survival Profile for Pathological Complete tumor & Nodal Responders among both study groups in general:

19 months follow up	Vinorelbine, Cisplatin		Docetaxel, Gemcitabine		P-value
Disease free survival	8 patients	100%	11 patients	100%	**0.02***

***:** statistically significant difference.

Table (2) shows that the **Disease Free Survival (DFS)** for those who had pathological complete tumor & nodal response after receiving either **(Vinorelbine, Cisplatin)** or **(Docetaxel, Gemcitabine)** regimens during 19 months of follow-up was 100% with significant statistical difference.

4. Discussion

This study revealed that 45 patients were randomized to have (4) cycles of (Vinorelbine, Cisplatin) and Clinical Tumor Response was assessed after that, and revealed that: 15 (33.33%) patients had Clinical Complete Tumor Response (cCR) to which they did Modified Radical Mastectomy (MRM). 23 (51.11%) patients had Clinical Partial Tumor Response (cPR) to which they received (2) additional cycles of the same regimen to which 4 more patients had reached Clinical Complete Tumor Response (cCR) and 19 (42.22%) patients remained partially responded to chemotherapy given (Partial Maintained). So that Clinical Complete Tumor Response (cCR) was achieved in 19 (42.22%) patients ($P < 0.01$) after having (Vinorelbine, Cisplatin) regimen which was more superior to what was stated by other studies previously listed in the research. The Response Rate (RR) for the (Vinorelbine, Cisplatin) regimen as 1st line treatment was (84.44%) ($P < 0.01$) which was comparable to what was stated by other studies previously listed in the research. Clinical Complete Nodal Response (cCR) for those who had +ve clinical lymphadenopathy at entry & had received (Vinorelbine, Cisplatin) was 19 (63.33%) patients ($P < 0.01$).

8 (17.77%) patients had Pathological Complete Tumor Response (pCR) ($P < 0.01$) out of 19 patients who had Clinical Complete Tumor Response (cCR) & out of 45 patients who had received (Vinorelbine, Cisplatin) regimen which was more superior & comparable to what was stated by other studies previously listed in the research, but 11 (24.44%) patients had Pathological Invasive Disease after doing Modified Radical Mastectomy. Pathological Complete Nodal Response (pCR) for those who had Clinical Complete Nodal Response after having (Vinorelbine, Cisplatin) regimen was 7 (36.84%) patients ($P = 0.02$) which was more superior & comparable to what was stated by other studies previously listed in the research.

The Haematological Side Effects happened for those who had (Vinorelbine, Cisplatin) were uncommon that Neutropenia Grade 2 & Grade 3 occurred in 7 (10.06%) patients, 2 (3.03%) patients respectively which was comparable to what was stated other studies previously listed in the research. No Progressive Disease had happened to any of the studied patients at all which was in agreement with what was stated by other studies previously listed in the research.

This study revealed that 45 patients were randomized to have (4) cycles of (Docetaxel, Gemcitabine) and Clinical Tumor Response was assessed after that, and revealed that: 7 (15.55%) patients had Clinical Complete Tumor Response (cCR) to which they did Modified Radical Mastectomy (MRM). 17 (37.77%) patients had Clinical Partial Tumor Response (cPR) to which they received (2) additional cycles of the same regimen to which 1 more patient had reached Clinical Complete Tumor Response (cCR) and 16 (35.55%) patients remained partially responded to chemotherapy given (Partial Maintained). So that Clinical Complete Tumor Response (cCR) was achieved in 8 (17.77%) ($P < 0.01$) patients after having (Docetaxel, Gemcitabine) regimen which was comparable to what was stated by other studies previously listed in the research. The Response Rate (RR) for the (Docetaxel, Gemcitabine) regimen as 1st line treatment was (53.33%) ($P < 0.01$) which was comparable to what was stated by other studies previously listed in the research. Clinical Complete Nodal Response (cCR) for those who had +ve clinical lymphadenopathy at entry & had received (Docetaxel, Gemcitabine) was 23 (76.66%) patients ($P < 0.01$).

4 (8.88%) patients had Pathological Complete Response (pCR) ($P < 0.01$) out of 8 patients who had Clinical Complete Response (cCR) & out of 45 patients who had received (Docetaxel, Gemcitabine) regimen, but 4 (8.88%) patients had Pathological Invasive Disease after doing Modified Radical Mastectomy. Pathological Complete Nodal Response (pCR) for those who had Clinical Complete Nodal Response after having (Docetaxel, Gemcitabine) regimen was 11 (47.82%) patients ($P = 0.02$).

The Haematological Side Effects were more commonly happened with the patients who received (Docetaxel, Gemcitabine) in comparison to those received (Vinorelbine, Cisplatin). The most significant Haematological Side Effects occurred for the patients who had received (Docetaxel, Gemcitabine): 21(40.38%) patients had Grade 2 Anemia, 20 (38.4%) patients had Grade 2 Neutropenia. 11 (21.1%) patients had Grade 3 Neutropenia. which was comparable to what was stated other studies previously listed in the research.

This study revealed that Disease Free Survival (DFS) for those who had pathological complete tumor & nodal response after receiving either (Vinorelbine, Cisplatin) or (Docetaxel, Gemcitabine) regimens during 19 months of follow-up was 100% with significant statistical difference. Overall Survival (OS)

during 19 months of follow-up for Responders in general at both study groups was 100% with good performance status (P = 0.02) with significant statistical difference.

Conclusion

(Vinorelbine, Cisplatin) regimen was effective and well-tolerated in patients with Locally Advanced Breast Cancer (LABC) with Overall Response Rate (RR): (84.44%). (Docetaxel, Gemcitabine) regimen is an effective and fairly well-tolerated regimen for the treatment of Locally Advanced Breast Cancer (LABC) with Overall Response Rate (RR): (53.33%), but was lower than what was achieved with (Vinorelbine, Cisplatin) in this study.

Disease Free Survival (DFS) & Overall Survival (OS) for those who had pathological complete tumor & nodal response after receiving either (Vinorelbine, Cisplatin) or (Docetaxel, Gemcitabine) regimens during 19 months of follow-up were (100%) with significant statistical difference.

Pathological complete remission (pCR) to neoadjuvant chemotherapy (NCT) has been consistently associated with improved disease free survival (DFS) and overall survival (OS) and early clinical response usually correlates with high probability for pCR.

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References

1. Boulos S, Gadallah M, Neguib S, Breast screening in the emerging world: High prevalence of breast cancer in Cairo. Breast; 2005; 14:340e6.
2. Olivotto IA, Chua B, Allan SJ, Long-term survival of patients with supraclavicular metastases at diagnosis of breast cancer. J Clin Oncol 2003; 21:851–4.
3. Brito RA, Valero V, Buzdar AU, Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: the University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol 2001; 19:628–33.
4. Singletary SE, Allred C, Ashley P, Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002; 20:3628–36.
5. National Cancer Data Base, 1998–2004. Available at: http://web.facs.org/ncdbbmr/ ncdbbenchmarks8.cfm. Accessed March 1, 2007.
6. Haagensen C, Stout A., Carcinoma of the breast II. Criteria of operability. Ann Surg 1943; 118:859.
7. Harris JR, Sawicka J, Gelman R, Management of locally advanced carcinoma of the breast by primary radiation therapy. Int J Radiat Oncol Biol Phys 1983; 9:345–9.
8. Rao DV, Bedwinek J, Perez C, Prognostic indicators in stage III and localized stage IV breast cancer. Cancer 1982; 50:2037–43.
9. Rubens RD, Armitage P, Winter PJ, Prognosis in inoperable stage III carcinoma of the breast. Eur J Cancer 1977; 13:805–11.
10. Townsend CMJr, Abston S, Fish JC., Surgical adjuvant treatment of locally advanced breast cancer. Ann Surg 1985; 201:604–10.
11. Arnold DJ, Lesnick GJ., Survival following mastectomy for stage III breast cancer, Am J Surg 1979; 137:362–6.
12. Montague ED, Fletcher GH., Local regional effectiveness of surgery and radiation therapy in the treatment of breast cancer. Cancer 1985; 55:2266–72.
13. Wolmark N, Wang J, Mamounas E, Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001; 96–102.
14. Mauriac L, Durand M, Avril A, Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. Results of a randomized trial in a single centre. Ann Oncol 1991; 2:347–54.
15. Mauriac L, MacGrogan G, Avril A, Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Institut Bergonie Bordeaux Groupe Sein (IBBGS). Ann Oncol 1999; 10:47–52.
16. Schwartz GF, Birchansky CA, Komarnicky LT, Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast Cancer 1994; 73:362–9.
17. Schwartz GF, Lange AK, Topham AK., Breast conservation following induction chemotherapy for locally advanced carcinoma of the breast (stages IIB and III). A surgical perspective. Surg Oncol Clin N Am 1995; 4:657–69.
18. Powles TJ, Hickish TF, Makris A, Randomized trial of chemo endocrine therapy started before or after surgery for treatment of primary breast cancer. J Clin Oncol 1995; 13:547–52.
19. Makris A, Powles TJ, Ashley SE, A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. Ann Oncol 1998; 9:1179–84.
20. Fisher B, Brown A, Mamounas E, Effect of preoperative chemotherapy on local– regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997; 15:2483–93.
21. Marie Catherine Lee, Lisa A. Newman, Management of Patients with Locally Advanced Breast Cancer: Surg Clin N 2007, Am 87, 379–398.
22. Samant R, Ganguly P., Staging investigations in patients with breast cancer: the role of bone scans and liver imaging. Arch Surg 1999; 134:551–3.

23. Mamounas E., Preliminary results of the NSABP B-27 Trial. Presented at the San Antonio Breast Cancer Symposium December 2001. San Antonio (TX).
24. Green M, Buzdar AU., Results from a prospective trial of neoadjuvant paclitaxel and doxorubicin for breast cancer. Presented at the American Society of Clinical Oncology May 2002 Symposium. Orlando (FL).
25. Dixon JM, Anderson TJ, Miller WR., Neoadjuvant endocrine therapy of breast cancer: a surgical perspective. Eur J Cancer 2002; 38:2214–21.
26. Ellis M, Coop A, Singh B., Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1 and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001; 19:3808–16.
27. Shamseddine A, Khalifeh M, Chehal A, Saliba T, Mourad YA, Taher A, Jalloul R, Bitar N, Dandashi A, Abbas J, Geara FB, A clinical phase II study of cisplatinum and vinorelbine (PVn) in advanced breast carcinoma (ABC): Department of Internal Medicine, American University of Beirut, Beirut, Lebanon. as04@aub.edu.lb: Am J Clin Oncol. 2005 Aug; 28(4):393-8.
28. Del Mastro L., Venturini M., Lionetto R., Carnino F., Guarneri D., Gallo L., Contu A., Pronzato P., Vesentini L., Bergaglio M., Comis S., Rosso R., Accelerated-intensified cyclophosphamide, epirubicin, and fluorouracil (CEF) compared with standard CEF in metastatic breast cancer patients: results of a multicenter, randomized Phase III study of the Italian Gruppo Oncologico Nord-Ouest-Mammella Inter Gruppo Group. J. Clin. Oncol. 2001, 19*:* 2213-2221.
29. Piccart M. J., Awada A., State-of-the-art chemotherapy for advanced breast cancer. Semin. Oncol. 2000, 27 (Suppl. 9)*:* 3-12.
30. Slamon D. J., Leyland-Jones B., Shak S., Fuchs H., Paton V., Bajamonde A., Flemming T., Eiermann W., Wolter J., Pegram M., Baselga J., Norton L., Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over-expresses HER2. N. Engl. J. Med. 2001, 344*:* 783-792.
31. Anderson H., Lund B., Bach F., Thatcher N., Walling J., Hansen H. H., Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: a Phase II study. J. Clin. Oncol. 1994, 12*:* 1821-1826.
32. Carmichael J., Fink U., Russell R. C. G., Spiettle M. F., Harris A. L., Spiessi G., Blatter J., Phase II study of gemcitabine in patients with advanced pancreatic cancer. Br. J. Cancer 1996, 73: 101-105.
33. Ulrich-Pur H., Kornek G. V., Raderer M., Haider K., Kwasny W., Depisch D., Greul R., Schneeweiss B., Krauss G., Funovic J., Scheithauer W., A Phase II trial of biweekly high dose gemcitabine for patients with metastatic pancreatic adenocarcinoma. Cancer (Phila.) 2000, 88: 2505-2511.
34. Lund B., Hansen O. P., Theilade K., Hansen M., Neijt J. P., Phase II study of gemcitabine (2′, 2′-difluorodeoxycytidine) in previously treated ovarian cancer. J. Natl. Cancer Inst. 1994, 86*:* 1530-1533.
35. Haider K., Kornek G. V., Kwasny W., Weinländer G., Valencak J., Lang F., Püribauer F., Kovats E., Depisch D., Scheithauer W., Treatment of advanced breast cancer with gemcitabine and vinorelbine plus human granulocyte colony-stimulating factor. Breast Cancer Res. Treat. 1999, 55*:* 203-211.
36. Carmichael J., Possinger K., Philip P., Beykirch M., Kerr H., Walling J., Harris AL., Advanced breast cancer: a Phase II trial with gemcitabine. J. Clin. Oncol. 1995, 13*:* 2731-2736.
37. Spielmann M., Llombart-Cussac A., Kalla S., Espie M., Namer M., Ferrero J. M., Dieras V., Fomoleau P., Cuvier C., Perrocheau G., Ponzio A., Kayitalire L., Pouillart P., Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology 2001, 60*:* 303-307.
38. Nabholtz J. M., The role of taxanes in the management of breast cancer. Semin. Oncol. 1999, 26 (Suppl. 8)*:* 1-3.
39. Rowinsky E. K., The development and clinical utility of the taxane class of anti microtubule chemotherapy agents. Annu. Rev. Med. 1997, 48: 353-374.
40. Hejna M., Kornek G. V., Raderer M., Ulrich-Pur H., Fiebiger W., Marosi L., Schneeweiss B., Greul R., Scheithauer W., Treatment of patients with advanced non-small-cell lung carcinoma using docetaxel and gemcitabine plus granulocyte-colony stimulating factor. Cancer (Phila.) 2000, 89*:* 516-522.
41. Georgoulias V., Kouroussis C., Androulakis N., Kakolyris S., Dimopoulus M. A., Papadakis E., Bouros D., Apostolopoulou F., Papadimitriou C., Agelidou A., Hatzakis K., Kalbakis K., Kotsakis A., Vardakis N., Vlachonicolis J., Front-line treatment of advanced non-small cell lung cancer with docetaxel and gemcitabine: a multicenter Phase II trial. J. Clin. Oncol. 1999, 17*:* 914-920.
42. Mavroudis D., Malamos N., Alexopoulus A., Kourousis C., Agelaki S., Sarra E., Potamianou A., Kosmas C., Rigatos G., Giannakakis T., Kalbakis K., Apostolaki F., Vlachonicolis J., Kakolyris S., Samonis G., Georgoulias V., Salvage therapy in anthracycline-pretreated metastatic breast cancer patients with docetaxel and gemcitabine: a multicenter Phase II trial. Ann. Oncol. 1999, 10*:* 211-215.
43. Frasci G., Comella P., D'Aiouto G., Thomas R., Capasso I., Elmo M., Botti G., Cortino G. R., Lapenta L., De Rosa V., Vallone P., Petrillo A., Comella G., Weekly docetaxel plus gemcitabine or vinorelbin e in refractory advanced breast cancer patients: a parallel dose-finding study. Ann. Oncol. 2000, 11*:* 367-371.