ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com
Journal DOI: 10.21474/IJAR01

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

METRONOMIC CHEMOTHERAPY (CAPECITABINE) IN WOMEN WITH TRIPLE- NEGATIVE OPERABLE BREAST CANCER.

Lobna A. Abdelaziz[1], Ahmed Z Al Attar[1],Shereen ElShorbagy[2]

1. Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
2. Medical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Manuscript Info

Manuscript History:

Received: 19 March 2016
Final Accepted: 22 April 2016
Published Online: May 2016

Key words:
Triple negative breast cancer,Metronomic chemotherapy,Capecitabine, Extended adjuvant treatment

Corresponding Author

Lobna A. Abdelaziz .

Abstract

Background:- Triple-negative breast cancer has negative estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2-neu) which constitute about 15%–20% of all breast cancers, it has highly aggressive nature ,high rates of relapse, visceral and central nervous system (CNS) metastasis. Targeted drugs like endocrine therapy or anti-(HER2-neu) don't have a role in TNBC patients .But cytotoxic chemotherapy is still the golden standard treatment for TNBC patients, despite the promise of new targeted and biologic agents. Metronomic chemotherapy, is frequent administration of certain cytotoxic agents with low doses at close regular intervals with no prolonged drug-free interruptions, can be given after standard adjuvant therapy in triple -negative disease

Aim:- The aim of this study was to evaluate the tolerability and efficacy of metronomic capecitabine which was given for one year after standard adjuvant treatment as an extended adjuvant therapy for women with triple-negative breast cancer.

Patients and Method:- Between January 2011 and November 2012, 22 women patients with pathologically proven operable breast cancer and immunohistochemistry proven triple negative{estrogen receptor (ER) ,progesterone receptor(PR) negative and HER 2 neu 0 or 1} , were enrolled to this prospective phase II study at Clinical Oncology Department and Nuclear Medicine , and Medical Oncology Department, Zagazig University ,Egypt. The patients received standard adjuvant anthracycline based chemotherapy (FAC, FEC, AC), or sequential anthracycline containing chemotherapy with taxanes followed by radiotherapy if indicated. Then the patients received 1 year of metronomic chemotherapy {oral capecitabine (Xeloda)} by a dose of (650 mg/m2, twice daily) which is discontinued if disease progression or major toxicities occurred. The primary endpoints of this study were relapse-free survival (RFS) and safety profile. The secondary end point was overall survival (OS).

Results:-At time of analysis, the median follow up duration was 34.5 months (range; 13-53 months) .Metronomic Capecitabine was well tolerated and no dose reduction needed in our study . The most common non hematological toxicity was hand foot syndrome which occurred in 4 (18.18%) patients, two of them were G1/2, and the other two were G3/4 who needed dose delay for one week .The second most common toxicity was G1/2 nausea and vomiting which was occurred in 3(13.6%) patients, and two patients had G3 diarrhea (9.09%) who needed admission. Hematological toxicity occurred in five (22.7%) patients

in the form of anaemia . No patients lost follow up. One patient (4.5%) had locoregional recurrence. Distant metastasis occurred in 4 (18.18%) patients. Three patients (13.6%) died during the follow up period. 3y OS was 86.4%. 2-3yDFS was 86.4% and 81% respectively.

Conclusion:- metronomic capecitabine after standard adjuvant therapy is effective and well tolerated in TNBC, but the effect of this regimen is still need a randomized phase III study on larger number of patients and longer follow up period .

Introduction:-

Breast cancer is considered the most frequently diagnosed female cancer worldwide **(1-2).**Triple-negative breast cancers has negative estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2- neu) and considered as a heterogenous disease, as it has different intrinsic molecular subtypes so it has different response to different treatment options **(3)** .Approximately 15%–20% of all breast cancer patients belong to this phenotype, it has highly aggressive nature, high rates of relapse, visceral and central nervous system (CNS) metastasis**(4).**

Clinicopathologic features of TNBC included large tumor size, young age , high grade and higher incidence of node positivity at presentation **(5-9).**Targeted drugs like endocrine therapy or trastuzumab don't have any role in TNBC patients **(4).** Cytotoxic chemotherapy is still the golden standard treatment for TNBC. The chemotherapy can be used as neoadjuvant or adjuvant treatment, and also can be used in metastatic TNBC patients **(10,11).**

Metronomic chemotherapy is frequent administration of certain cytotoxic agents at low dose, at close regular intervals with no prolonged interruptions. Many trials on patients with triple-negative breast cancer are assessing the metronomic chemotherapy regimen after receiving standard adjuvant therapy, which showed a good benefit from this treatment. Metronomic chemotherapy has low cost so it can be used widely, especially in developing countries **(12).**

Capecitabine is an orally administered 5 Flurouracil (5-FU) prodrug which is converted to 5-FU in tumor tissue more than normal tissue due to high level of thymidine phosphorylase enzyme. Thus; capecitabine has relatively selective cytotoxicity for tumor tissue. It can be given alone as a monotherapy in many tumor types and also in combination with other agents .Single-agent capecitabine can be used in breast cancer which is refractory to anthracyclines and taxanes, with response rates up to 15%–29% and stable disease in 31%–46% **(13).**

A small, randomized, phase III trial has concluded that capecitabine can be used as first-line treatment for metastatic breast cancer. In this trial, the patients were randomized into two arms .One arm received capecitabine and the other one received CMF (cyclophosphamide, methotrexate, and 5-FU), the results showed that the response rate with capecitabine was 30% versus 16% for intravenous CMF. The median survival in the capecitabine group was 21.6 months compared to 17.2 months in the CMF group, with no statistical difference between both groups **(14).**

Many trials were done to test the reduction of cabecitabine dose and its effect on clinical outcome in metastatic breast cancer patients. The results of these trials suggested that the dose of capecitabine can be reduced to minimize toxicity with no compromising the response**,** duration of response, time to treatment failure or overall survival**(14).**

CIBOMA 2004-01/GEICAM 2003-11 is a phase III ,multicenter, randomized trial evaluating the efficacy of maintenance chemotherapy with capecitabine after standard adjuvant anthracycline and/or taxane-containing chemotherapy in TNBC patients who were operable and had positive lymph node or negative lymph node with tumor diameter 1 cm. This trial was divided into two arms (A and B),arm A received eight cycles of standard dose capecitabine (1000 mg/m^2 bid, d1–14 q21d) not metronomic dose and arm B was kept on observation. The primary endpoint is disease-free survival .In San Antonio cancer symposium 2010 ,the first safety data of this

randomized trial was published by **Lluch et al** and It revealed that more than 75% of the patients continued their planned treatment and about 15% of the patients discontinued their treatment due to toxicity or withdrawal **(15,16,17)** . Another randomized phase III trial evaluating the efficacy of extended adjuvant capecitabine treatment in TNBC is **SYSCBS-001** trial, the patients in the first arm (arm A) received standard adjuvant chemotherapy followed by observation and the second arm (arm B) received 1 year of extended adjuvant Capecitabine with a metronomic dose (650 mg/m2 twice every day) after standard adjuvant chemotherapy. No published results about this trial until now **(18).**

In view of previous two trials, we planned our trial to study the tolerability, safety and survival in women with operable TNBC, who received capecitabine for one year after standard adjuvant therapy, and we chose the metronomic dose used in **SYSCBS-001** trial as it is low dose with low cost and expected to be more tolerable with less toxicity.

Patients and method:-

Between January 2011 and November 2012, 22 women patients with pathologically proven operable breast cancer and immunohistochemistry proven triple- negative{estrogen receptor (ER) ,progesterone receptor(PR) negative and HER 2 neu 0 or 1} ,positive lymph node (LN) or negative LN with tumor size ≥1cm pathologically, were enrolled to this prospective phase II study at Clinical Oncology Department and Nuclear Medicine , Medical Oncology Department . Zagazig University, Egypt. The eligibility criteria were : – All patients had operable, breast cancer ,age (18-65 years), performance status (PS) was 0-2 according to Eastern Cooperative Oncology Group (ECOG) , adequate CBC,LFT,KFT with baseline laboratory criteria included hemoglobin >9.0 g/dL, WBC $\geq 3.5x10^9$ /L, neutrophils $\geq 1.5\times10^3$/mL, platelet count $\geq 100\times10^3$/mL, creatinine ≤ 2 mg/ML ,total bilirubin level less ≤1.5 the upper limit of normal; alanine aminotransferase (ALT),asparate aminotransferase(AST) ≤3 the upper limit of normal. Patients should have normal cardiac function { left ventricular ejection fraction (LVEF) ≥60}.

The exclusion criteria were, patients with T4and N3 breasr cancer , patients who have distant metastasis, secondary malignancy, pregnancy or concurrent serious and uncontrolled medical comorbidity (e.g. clinically significant cardiac disease, persistent immune-compromised states, uncontrolled infection). Informed consent was obtained in all cases; the study protocol was approved by the Ethical Committee of Faculty of Medicine, Zagazig University.
The staging procedures were medical history, clinical and local examination, mammography, chest X-ray and pelviabdominal ultrasonography and /or computed tomography(CT) scans if needed , complete blood picture(CBC) with differential count , renal function test (RFT) and liver function test(LFT).Bone scan and CT brain were done if indicated .
The patients received standard adjuvant anthracycline based chemotherapy (FAC, FEC, AC), or sequential anthracycline containing chemotherapy with taxanes followed by radiotherapy if indicated. Then the patients received 1 year of metronomic chemotherapy {oral capecitabine (Xeloda)} by a dose of (650 mg/m2, twice daily) which is discontinued if disease progression or major toxicities occured. The adverse events were assessed throughout the study. During capecitabine , the patients were followed up monthly by history and physical examination ,CBC with differential count , RFT and LFT .if sever hematological and non hematological adverse events occurred ,the Capecitabine would be delayed for 1-2 weeks. Chest x ray and pelviabdominal US were done every three months for two years after standard adjuvant therapy with CT if needed, and every six months after that. Mammography and breast ultrasound of the contralateral breast or both breasts (if breast conservative surgery was done) were done anually. CT brain and bone scan were done when indicated. Toxicity grading was done by using the common terminology criteria for adverse event (NCI-CTC, version 3.0)**(19).**

Outcome Measure and statistical analysis:-

The primary endpoints of this study were relapse-free survival (RFS) and safety profile. The secondary end point was overall survival (OS). Statistical analysis was done by using SPSS [Statistical package] (version 22). RFS was calculated as the time from end of treatment to the time at which local recurrence/distant metastasis was detected or most recent follow up at which local recurrence /distant metastasis was not detected (censored).It is estimated by using the Kaplan–Meier method. OS was calculated as the time from diagnosis to death or the most recent follow-up visit (censored), it is estimated by using the Kaplan–Meier method too . Chi square (X^2) test was used .All tests are two sided and the results were considered significant if ($P < 0.05$).

Results:-

Twenty two (22) women patients with pathologically proven operable breast cancer and immunohistochemistry proven triple -negative(ER ,PR negative and HER 2 neu 0 or 1) , were enrolled in this prospective phase II study.The patients and tumor characteristics are presented in the following table (Table 1).

Table 1:- Patients and tumor characteristics.

		Frequency	Percent (%)
Age mean ±SD	48.22±11.76		
Menopausal status	Post	**13**	**59.1**
	Pre	**9**	**40.9**
Family history	-ve	**17**	**77.3**
	+ve	**5**	**22.7**
Pathological type	IDC	**19**	**86.4**
	ILC	**3**	**13.6**
Grade	G1	**6**	**27.3**
	G2	**6**	**27.3**
	G3	**10**	**45.5**
Tumor size	T1	**3**	**13.6**
	T2	**13**	**59.1**
	T3	**6**	**27.3**
LN status	N0	**6**	**27.3**
	N1	**11**	**50.0**
	N2	**5**	**22.7**
Lymphovascular invasion(LVI)	-ve	**14**	**63.63**
	+ve	8	**36.36**
Perineural invasion	-ve	**18**	**81.81**
	+ve	**4**	**18.18**
Surgical margin	-ve	**19**	**86.4**
	+ve	**3**	**13.6**
Extracapsular extension	-ve	**15**	**68.2**
	+ve	**7**	**31.8**
Tumor side	Lt	**10**	**45.5**
	Rt	**12**	**54.5**
Extra and intraductal component	**No**	**16**	**72.7**
	Yes	**6**	**27.3**
PS	**0**	**18**	**81.8**
	1	**2**	**9.1**
	2	**2**	**9.1**
Type of surgery	**BCS**	**5**	**22.7**
	MRM	**17**	**77.3**
Adjuvant Radiotherapy	**No**	**10**	**45.5**
	Yes	**12**	**54.5**
Type of chemotherapy	**Anthracyclin**	**10**	**45.5**
	Anthracyclin+ Taxane	**12**	**54.5**
	Total	**22**	**100.0**

The mean age of patients was 48.22 ±11.76, the median age was 48.5 years (range 27.0-67.0 years).Thirteen (59.1%) patients were postmenopausal and 9 (40.9%) patients were premenopausal.17 (77.3%) patients had negative family history whereas only 5 (22.7%) had positive family history. The invasive ductal carcinoma constituted the vast majority of the patients which was present in 19(86.4%) patients, whereas invasive lobular carcinoma was present in only 3(13.6%) patients. Grade I and grade II disease were equally distributed, each of them was present in 6(27.3%) patients, while GIII was present in 10 (45.5%) patients.T1 disease was present in 3 patients (13.6%), 13 patients (59.1%) had T 2 disease at initial presentation and 6 (27.3%) patients had T3 disease .six (27.3%)patients had N0, 11 (50.0%)patients had N1 and 5(22.7%)patients had N2. Fourteen patients (63.63%) had negative

lymphovascular invasion and 8 (36.36%) patients had positive lymphovascular invasion. Eighteen patients (81.81%) had negative perineural invasion whereas 4 (18.18%) patients had positive perineural invasion.Most of the patients (86.4%) and (68.2%) had negative surgical margin and negative extracapsular extension respectively .Twelve patients (54.5%)had RT sided breast cancer whereas ten (45.5) patients had Lt sided breast cancer.extra and intraductal component was present in 6 (27.3%) patients .Eighteen patients (81.8%) had performance status score (PS) 0 but only two (9.1%) had each of PS 1 and 2. Seventeen patients (77.3%) underwent modified radical mastectomy (MRM), and five patients (22.7%) underwent breast conserving surgery(BCS). 12 (54.5%) patients had adjuvant radiation therapy according to the indication.10(45.5%) patients received anthracyclin containing adjuvant chemotherapy and 12 (54.5%) patients received taxanes containing chemotherapy. The last patient finished his adjuvant treatment on April 2013 and finished 1year metronomic chemotherapy on April 2014.

Table (2) showed correlation between patients and tumor characteristics and the development of metastasis,
It revealed that there is significant correlation between development of metastasis and premenopausal status(P=0.043) , positive lymphovascular invasion(P= 0.005) ,N2 (P= 0.00),G3 (P= 0.021), RT side (P= 0.02),extracapsular extension (P=0.00).

Table 2:- correlation between patients and tumor characteristics and the development of metastasis.

			Metastasis		Total	X^2	P
			NO	YES			
Menopausal	Post	No	**12**	**1**	**13**	**4.09**	**0.043***
		%	**70.6%**	**20.0%**	**59.1%**		
	Pre	No	**5**	**4**	**9**		
		%	**29.4%**	**80.0%**	**40.9%**		
Lymphovascu-lar invasion	-ve	No	**14**	**0**	**14**	**7.76**	**0.005***
		%	**87.5%**	**0.0%**	**63.63%**		
	+ve	No	**2**	**6**	**8**		
		%	**12.5%**	**100.0%**	**36.36%**		
LN	N0	No	**6**	**0**	**6**	**22.0**	**0.00****
		%	**35.3%**	**0.0%**	**27.3%**		
	N1	No	**11**	**0**	**11**		
		%	**64.7%**	**0.0%**	**50.0%**		
	N2	No	**0**	**5**	**5**		
		%	**0.0%**	**100.0%**	**22.7%**		
Grade	G1	No	**6**	**0**	**6**	**7.76**	**0.021***
		%	**35.3%**	**0.0%**	**27.3%**		
	G2	No	**6**	**0**	**6**		
		%	**35.3%**	**0.0%**	**27.3%**		
	G3	No	**5**	**5**	**10**		
		%	**29.4%**	**100.0%**	**45.5%**		
Side	Lt	No	**10**	**0**	**10**	**5.3**	**0.02***
		%	**66.66%**	**0.0%**	**45.5%**		
	Rt	No	**5**	**7**	**12**		
		%	**33.33%**	**100.0%**	**54.5%**		
Extracapsular extension	No	No	**15**	**0**	**15**	**17.25**	**0.00****
		%	**93.75%**	**0.0%**	**68.2%**		
	Yes	No	**1**	**6**	**7**		
		%	**6.25%**	**100.0%**	**31.8%**		

Toxicity:-

Metronomic capecitabine was well tolerated and no dose reduction needed in our study . The toxicity is presented in the following table (Table 3).The most common non hematological toxicity was handfoot syndrome which occurred in 4 (18.18%) patients ,two of them was G1/2 and the other two were G3/4 who need dose delay for one week .The second most common toxicity was G1/2 nausea and vomiting which was occurred in 3(13.6%) patients .two patients had G3 diarrhea(9.09%) who needed hospital admission .Hematological toxicity occurred in five (22.7%) patients in the form of anaemia.

Table 3 :- The toxicity of TNBC who received metronomic chemotherapy after standard adjuvant treatment

	G1/2		G3/4		Total	
	No	**%**	No	%	No	%
1-Hand foot syndrome	**2**	**9.09**	**2**	**9.09**	**4**	**18.18**
2-diarrhea	**-**	**-**	**2**	**9.09**	**2**	**9.09**
3-nausea and vomiting	**3**	**13.6**	**-**	**-**	**3**	**13.6**
4-Anaemia	**5**	**22.7**	**-**	**-**	**5**	**22.7**

Survival and metastasis:-

The median follow up period was 34.5 months (range:13-53 months) . No patients were lost during follow up period .One patient had locoregional recurrence.Distant metastasis occurred in 4 (18.18%) patients in the form of liver metastasis(1 patient) and pulmonary metastasis (1patient),intracranial(CNS) metastasis (1 patient),both pulmonary and CNS metastasis (1 patient) .Three patients(13.6%) died. By using Kaplan-Meier method , we found that the Mean RFS was 37.89(±2.13) months with 95% confidence interval {CI 95%}(33.72-42.06).The median RFS not reached yet.2-3y RFS was 86.4% and 81% respectively. Mean OS was47.77(±2.81) months with 95% confidence interval {CI 95%}(42.27-53.27) ,the median OS not reached yet , 3 y OS was 86.4% . (Figure 1,2).

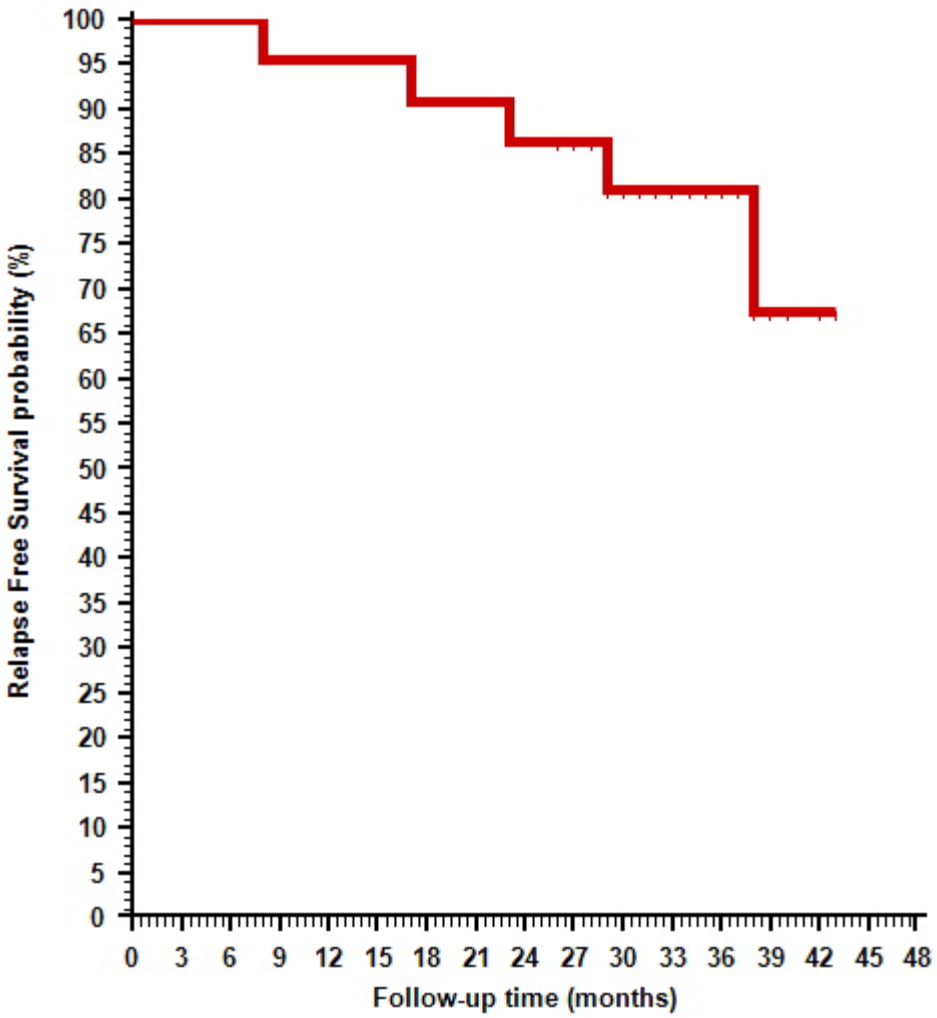

Figure (1): Kaplan Meier curve of relapse free survival (months).

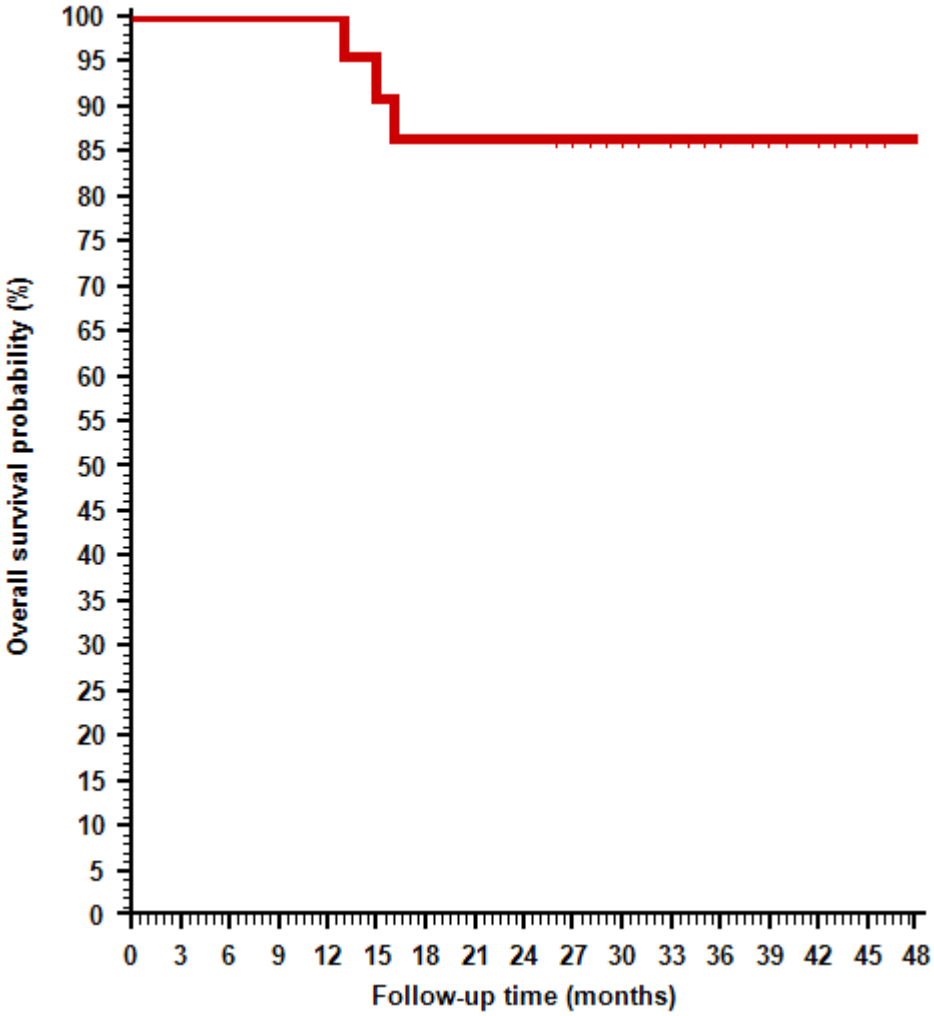

Figure (2): Kaplan Meier curve of overall survival (months).

Discussion:-

TNBC patients had benefit from anthracyclines and/or taxanes based adjuvant chemotherapy in many large randomized trials .But there are also other new chemotherapy agents such as capecitabine, platinum-based agents (especially for patients with germline mutations in the BRCA1 gene) and ixabepilone **(20-23).**

Vascular endothelial growth factors (VEGF), EGFR are overe-xpressed in TNBC patients and also there are a high rate of BRCA mutation or deficiency in BRCA function. So VEGF inhibitors, EGFR inhibitors, poly ADP-ribose polymerase inhibitors, and mammalian target of rapamycin inhibitors can be used in treatment of TNBC **(24).**

Hormonal treatment is given in the first 5 years after adjuvant chemotherapy with or without the anti-Her2 therapy (Trastuzumab) in non TNBC patients ,But in TNBC patients,they can't receive these agents .So there is high risk of relapse and distant metastasis in TNBC patients . So the augmentation of the initial response and its consolidation with a maintenance therapy with low dose which is not toxic to the patients with no prolonged, drug-free breaks is needed. **(24,25).**

metronomic chemotherapy , by using (capecitabine) was used in metastatic breast cancer and also can be used for non metastatic breast cancer patients after receiving their adjuvant treatment as an extended adjuvant therapy **(26-27).**

There are different interpretations of the mechanism of action of metronomic chemotherapy. It may act by reducing the circulating VEGF concentration thus it causes inhibition of tumor angiogenesis, or by inducing apoptotic death of endothelial cell in tumor microvasculature **,**or by stimulation of the immune response because they induce reduction in circulating regulatory T cells which is associated with suppression of the inhibitory functions on conventional T and natural killer cells, thus peripheral T-cell proliferation and innate killing activities are restored **(28,29).**

The results of our study showed that the most common non hematological toxicity was handfoot syndrome which occurred in 4 (18.18%) patients ,two of them were G3/4 who needed postponing oh their treatment for one week .The second most common non hematological toxicity was G1/2 nausea and vomiting which was occurred in 3(13.6%) patients. Two patients had G3 diarrhea(9.05%) who needed hospitalization .Hematological toxicity occurred in five (22.7%) patients in the form of anaemia.No patient needed reduction of treatment dose in our trial .One patients had locoregional recurrences.Four (18.18%) patients had distant metastasis ,in the form of liver metastasis, pulmonary metastasis, intracranial(CNS) metastasis and both pulmonary and CNS metastasis one patient for each of them. Regarding the survival ,Three patients (13.6%) died during the follow up period. Mean RFS was 37.89(±2.13) months with 95% confidence interval {CI 95%}(33.72-42.06).The median RFS not reached yet.2-3y RFS was 86.4% and 81% respectively. Mean OS was47.77(±2.81) months with 95% confidence interval {CI 95%}(42.27-53.27) ,the median OS not reached yet , 3 y OS was 86.4% . There was significant correlation between development of metastasis and premenopausal status(P=0.043) , positive lymphovascular invasion(P= 0.005) ,N2 (P= 0.00),G3 (P =0.21), RT side (P= 0.02),extracapsular extension (P=0.00) but this significancy may be because of small number of patients and short follow up period .So I recommend to study this regimen in a phase III randomized trial on larger number of patients with longer follow up period.

A phase II trial done by **Ezz El-Arab et al (30**) on 60 patients with metastatic breast cancer who received low dose capecitabine 500 mg two times per day and with oral cyclophosphamide (CTX)50 mg once daily . Assessment of disease control rate and its relation with percentage VEGF was the primary end point of this study, the secondary objective was Assessment of toxicity profile, time to disease progression and overall survival. The median follow-up period was 16 months (ranged from 4 to 38 months). The median overall survival for all patients was 16 ± 8.02 months (95%CI 13.06–17.28 months) , for complete and partial responders was 24 ± 10.01 months (95% CI 17.08–28.63 months) and for stable disease was 19 ± 8.12 months (95%CI 16.08–18.65 months). The median time to progression was 7 ± 2.59 months (95% CI 6.93–9.93) for whole group . The treatment protocol was well tolerated. The most common side effect was G1/2 Palmar–plantar erythrodythesia and was present in(36.7% of patients). The most common hematological toxicity was G1/2 Leucopenia which was present in 30.3% of patients while G3 occurred in only one patient(1.3%). 20% of patients had Grade 1/2 elevation of serum transaminases but 8% of the cases had G3 who needed transient stoping of Capecitabine and 50% reduction of the dose in the following cycles. 28.3% of patients had G1/2 nausea and vomiting ; while G1/2 diarrhea was observed in 20% of patients .

In Ezz El-Arab et al study, no patients had G3/4 hand –foot syndrome but **In our study**, hand –foot syndrome was the most common side effect which was observed in four (18.18%) patients ,two of them were G3/4 , this may be because they used lower dose of capecitabine in their trial. Nausea and vomiting in our study was lower than in their study ,it was 13.6% in comparison to 28.3% in their study (This may be due to effect of cyclophosphamide in their study). In our study ,diarrhea happened in two patient (9.09%) and it was lower than **Ezz El-Arab et al study** where it was 20% , it was G3/4 in our trial but in **Ezz El-Arab et al study** there was no G3/4 diarrhea (it could be because of lower dose of capecitabine in their trial also) . There was an elevation of serum transaminases (G3) in **Ezz El-Arab et al** study,it was about 8% of patients but in our study there was no increase of liver enzymes which may be because of addition of CTX to Xeloda in their study and also because the metastatic patients in their study may include patients with liver metastasis and the patients were also heavily pretreated.
Another trial was done by **Fedele et al (31**) on 60 metastatic breast cancer patients who received capecitabine (1500 mg once a day) as a metronomic chemotherapy . Hematologic toxicity was infrequent and mild. The most common adverse effects was Hand-foot syndrome (10%) and diarrhea (7%) ; vomiting was present in only 2% of the patients, and all toxicities were G1/2. Grade 3 hand-foot syndrome occurred in 3 patients .No hepatic toxicity was recorded.

CIBOMA and SYSCBS-001 are phase III trials which done on TNBC patients who received maintenance therapy (Capecitabine) as an extended adjuvant treatment after standard adjuvant chemotherapy**(15).**

CIBOMA 2004-01/GEICAM 2003-11 is a phase III ,multicenter, randomized trial evaluated the efficacy of maintenance chemotherapy with capecitabin after standard adjuvant anthracycline and/or taxane-containing chemotherapy in TNBC patients who were operable and had positive lymph node or negative lymph node with tumor diameter ⩾1 cm. This trial was divided into two arms (A and B),arm A received eight cycles of standard dose capecitabine (1000 mg/m^2 bid, d1–14 q21d) and arm B was kept on observation. The primary endpoint is disease-free survival . Because of lower dose of capecitabine used in our study ,most of the adverse effects are lower than CIBOMA trial **(16).**

In San Antonio cancer symposium 2010 ,the first safety data from this randomized phase III trial(CIBOMA 2004-01/GEICAM 2003- 11) was published by **Lluch et al**.It revealed that more than 75% of the patients continued their planned treatment and about 15% of the patients discontinued their treatment due to toxicity or withdrawal. Grade 3 or 4 adverse effects were higher in arm A , hand foot syndrome 17.4%, diarrhea 2.9%, vomiting 1.0%, and elevated bilirubin 1.0% . There were 7 serious adverse events related to capecitabine (3 patients had grade 2-4 diarrhea which necessitate hospitalization ; one patient had grade 2 thoracic pain, grade 2 arrhythmia occurred in one patient also, coronary vasospasm and chest pain occurred in 1 patient each) . No survival data are available of this ongoing trial until now **(17).**

Barrios CE et al presented an abstract in 2013 about **CIBOMA/2004-01_GEICAM/2003-11** showed that there were876 patients recruited in this randomized trial.This recruitment was completed in September 2011 and statistical assumptions showed expected recurrence risk reduction about 30% at 5 years (64.7% to 73.7%, HR 0.701) **(32).**

Another randomized phase III trial evaluating the efficacy of extended adjuvant capecitabine treatment in TNBC is **SYSCBS-001** trial .The patients in the first arm (arm A) received standard adjuvant chemotherapy followed by observation and the second arm (arm B) received 1 year of extended adjuvant Capecitabine (650 mg/m2 twice every day) after standard adjuvant chemotherapy. No published results about this ongoing trial until now **(18).**

A prospective phase II study done by **Shawky H and Galal S (2014)(33)** , on 19 patients with pathologically proven triple negative breast cancer . The patients received one year of oral capecitabine (Xeloda) metronomic therapy (650 mg/m2 , twice every day) after standard adjuvant chemotherapy.the median follow up duration was 30.1 months . Disease-free survival rate and safety profile were the primary endpoints of this study whereas the secondary end point was overall survival. 2-3 y DFS was 88.8% and 82.05% respectively. No patients had died and the median OS was not reached. Adverse events related to treatment were manageable .Three patients had hand – foot syndrome ,only one of them (5.3%) had Grade 3/4. 10.5% of the patients had diarrhea , (5.3% was for each Grade 1/2 and G3/4) .Two patients had G1/2 nausea and vomiting (10.5%).Fatigue was present in only one patient. Grade 3/4 hematologic toxicity was not recorded. No patient developed locoregional relapse. 3patients (15.8%) had distant metastases, one of them had intra-cranial disease metastases.

Grade 3/4hand foot syndrome in **Shawky H and Galal S (2014)** was lower than our study,(5.3 %versus 9.09%). Grade3 diarrhea was present in two patients (9.09%)in our study versus one patient in their study . Grade1/2 nausea and vomiting was present in 3 patients(13.6%) in our trial but in **Shawky H and Galal S (2014)** trial it was present in 2 patients(10.5%). (22.7%) of patients had hematological toxicity in our study versus (31.6%) in their study.One patient (4.5%) had locoregional recurrence in our study but no patients had locoregional recurrence in their trial. Distant metastasis occurred in three patients(15.8%) in their study versus four(18.18%) patients in our trial. There were three (13.6%)patients died in our study with the mean OS was47.77(±2.81) months with 95% confidence interval {CI 95%}(42.27-53.27) ,the median OS not reached yet ,3 y OS was 86.4% ,but in their trial no patients died . 2-3 y DFS in their study was (88.8%), (81.05%) respectively but in our trial 2-3 y RFS was (86.4%%),(81%) respectively. Mean RFS was 37.89(±2.13) months with 95% confidence interval {CI 95%}(33.72-42.06).

A prospective phase II study done by **Alagizy H et al(2015) (34)** on 41 TNBC patients between June 2010 and December 2013. They received capecitabine 500 mg PO twice daily and continuously for six months after finishing six cycles of adjuvant chemotherapy± postoperative radiotherapy.31.7% of patients had grade 1 palmar–plantar erythrodysesthesia ;whereas 12.2% of patients had grade 1 vomiting ; and grade 1 diarrhea was present in two patients (4.9%). Median follow-up duration was 34 months. Mean disease-free survival (DFS) was 42.4 months (95% CI, 39.02–45.79), while median DFS was not reached. Mean overall survival was 44.34 months (95% CI 41.9–46.9 .There was no G3/4 toxicity in **Alagizy H et al(2015)** trial ,only G1/2 toxicity, (this may be because of lower dose used in this trial than our trial). Grade 1 palmar–plantar erythrodysesthesia was present in 13 patients (31.7%) but in our trial G1/2 was found in two (9.09%)patients and G3/4was occurred in two(9.09%) patients too . In **Alagizy H et al(2015)** grade 1 vomiting was present in (12.2%) of the patients but in our study it was present in 13.6% ofb the patients . Two patients had G3/4 diarrhea in our trial but in **Alagizy H et al(2015)** there were two patients had grade 1 diarrhea (4.9%). In our study ,three patients (13.6%) died during the follow up period. Mean RFS was 37.89(±2.13) months with 95% confidence interval {CI 95%}(33.72-42.06).The median RFS not reached yet.2-3y RFS was 86.4% and 81% respectively. Mean OS was47.77(±2.81) months with 95% confidence interval {CI 95%}(42.27-53.27) ,the median OS not reached yet ,3 y OS were 86.4% , but in their study Estimated median follow-up duration was 34 months. Estimated mean disease-free survival (DFS) was 42.4 months (95% CI, 39.02–45.79), while median DFS was not reached. Estimated mean overall survival was 44.34 months (95% CI 41.9–46.9).

There is a phase III randomized trial **(The BEATRICE study**) was done on 2591 patients with TNBC .The patients was randomized into two arms ,the first arm received chemotherapy alone and the second arm received chemotherapy followed by a amaintenance treatment (bevacizumab) .Median follow-up was 31.5 months in the chemotherapy-alone group and 32.0 months in the bevacizumab group.The 3-year disease-free survival (DFS)was 82.7% (95% CI 80.5–85.0) in the first arm and 83.7% (81.4–86.0) in the second arm. .There were an increased incidences of grade 3 or worse hypertension in bevacezumab arm (12%) vs(1%) in chemotherapy arm, severe cardiac events occurring at any point during the 18-month safety reporting period (1% vs <0·5%)**(35).**

Conclusion:-

We conclude that, metronomic capecitabine after standard adjuvant therapy is effective and well tolerated in patients with TNBC but we recommend to study this regimen in a big phase III randomized trial with larger number of patients and longer follow up period .

References:-

1. Jemal A, Bray F, Center MM, et al:- Forman D. Global cancer statistics. CA Cancer J Clin ,2011;61(2):69–90.
2. Surveillance Epidemiology and End Results (SEER) :-Lifetime risk of developing or dying of cancer [webpage on the Internet] Bethesda, MD: Surveillance Research Program; nd. Available from: Accessed May 15, 2012
3. Foulkes WD, Smith IE, Sreis J,et al :- Triple-negative breast cancer, New England journal of medicine ,2010,363;20,1938-1948 .
4. Brouckaert O, Wildiers H, Floris G, et al :- Update on triple-negative breast cancer: prognosis and management strategies. Int J Womens Health,2012 ; 4: 511–520.
5. Rydén L, Jirström K, Haglund M ,et al :-Epidermal growth factor receptor and vascular endothelial growth factor receptor 2 are specific biomarkers in triple-negative breast cancer. Results from a controlled randomized trial with long-term follow-up. Breast Cancer Res Treat,2010, 120 (2) , pp. 491–498
6. Dent R, Trudeau M, Pritchard KI, et al :-Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res,2007 ;13:4429-34.
7. Lin NU, Vanderplas A, Hughes ME, et al :- Clinicopathological features and sites of recurrence according to breast cancer subtype in the National Comprehensive Cancer Network (NCCN). J Clin Oncol,2009 ;27:abstr 543.
8. Dawood S, Broglio K, Esteva FJ, et al :- Survival among women with triple receptor-negative breast cancer and brain metastases. Ann Oncol,2009 ;20:621-7.
9. Irvin WJ and Carey LA :-What is triple-negative breast cancer? Eur J Cancer,2008 ;44:2799-805.
10. Lund M, Butler E, Hair B, et al :- A first report of incidence rates (not prevalence) by breast cancer subtypes. Cancer Res,2009 ;69:3065.
11. Isakoff SJ :-Triple-negative breast cancer: role of specific chemotherapy agents .Cancer J,2010, 16 (1) , pp. 53–61
12. Joensuu H, and Gligorov J:- Adjuvant treatments for triple-negative breast cancers. Ann Oncol,2012, 23 (suppl 6):vi40-vi45.
13. Munzone E and Colleoni M :-Clinical overview of metronomic chemotherapy in breast cancer.Nat Rev Clin Oncol,2015,631-44

14. Hennessy BT, Gauthier AM , Michaud LB ,et al :- Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M. D. Anderson Cancer Center and a review of capecitabine toxicity in the literature .Annals of Oncology,2005 16: 1289–1296.
15. Metzger-Filho O, Tutt A, de Azambuja E, et al :- Dissecting the heterogeneity of triple-negative breast cancer. J Clin Oncol,2012 ;30(15):1879–87.
16. Group SBCR (2005): maintenance treatment with capecitabine versus observation in breast cancer patients (CIBOMA).
17. Lluch A, Gomez H, Ruiz-Borrego M, et al .: First safety data from a randomized phase III (CIBOMA 2004-01/GEICAM 2003-11) trial assessing adjuvant capecitabine maintenance therapy after standard chemotherapy for triple-negative early breast cancer, San Antonio Breast Cancer Symposium,2010: Abstract P5-10
18. University SY-s: efficacy of capecitabine metronomic chemotherapy to triple-negative breast cancer (SYSCBS-001), 2010.
19. Casuati D :-Toxicities of chemotherapy NCI common toxicity criteria version 3. In: Casciato D, editor. Manual of clinical oncology,2004, fifth ed., vol. 698. Philadelphia: Lippincott Williams and Wilkins; p. 703.
20. Cheang M, Chia SK, Tu D, et al:- Anthracyclines in basal breast cancer: The NCIC-CTG trial MA5 comparing adjuvant CMF to CEF. J Clin Oncol 2009;27:abstr 519.
21. Steger GG, Barrios C, O'Shaughnessy J, et al. Review of Capecitabine for the Treatment of Triple-Negative Early Breast Cancer [abstract PD01-03]. San Antonio, TX: San Antonio Breast Cancer Symposium; 2010.
22. O'Shaughnessy J, Paul D, Stokoe C, et al:- First efficacy results of a randomized, open-label, phase iii study of adjuvant doxorubicin plus cyclophosphamide, followed by docetaxel with or without capecitabine, in high-risk early breast cancer [abstract S4-2]. San Antonio, TX: San Antonio Breast Cancer Symposium; 2010.
23. Lluch A, Gomez H, Ruiz-Borrego M, et al:-First Safety Data from a Randomised Phase III (CIBOMA 2004-01/GEICAM 2003-11) Trial Assessing Adjuvant Capecitabine Maintenance Therapy after Standard Chemotherapy for Triple-Negative Early Breast Cancer. Cancer Res 2010;70:P5-10-15.
24. Sirohi B, Arnedos M, Popat S, et al:-Platinum-based chemotherapy in triple-negative breast cancer. Ann Oncol 2008;19:1847-52. [PubMed]
25. Turner N, Tutt A, Ashworth A:- Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer2004;4:814-19. [PubMed]
26. Cleere DW:- Triple-negative breast cancer: a clinical update. Community Oncol 2010;7:203-11.
27. Pasquier E, Kavallaris M, André N:-Metronomic chemotherapy: new rationale for new directions. Nat Rev Clin Oncol 2010;7:455-65. [PubMed]
28. Scharovsky OG, Mainetti LE, Rozados VR:- Metronomic chemotherapy: changing the paradigm that more is better. Curr Oncol 2009;16:7-15. [PMC free article] [PubMed]
29. Gasparini G. Metronomic scheduling:- the future of chemotherapy? Lancet Oncol 2001;2:733–40.
30. Ezz El-Arab L, Swellamb M, El Mahdy M. Metronomic chemotherapy in metastatic breast cancer: impact on VEGF. J Egypt Natl Canc Inst 2012;24(Suppl. 1):15–22]
31. Fedele P, Marino A, Orlando L, et al :- Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. Eur J Cancer,2012 ;48(1):24–9
32. Barrios CE, Lluch A, Ruiz-Borrego M:- Abstract OT3-1-06: CIBOMA/2004-01_GEICAM/2003-11: A randomised phase III trial assessing adjuvant capecitabine (Cap) maintenance therapy after standard chemotherapy for triple-negative early breast cancer (EBC) .Cancer Res ,2013;73(24 Suppl): Abstract nr OT3-1-06.
33. Shawky H and Galal S :- Preliminary results of capecitabine metronomic chemotherapy in operable triple-negative breast cancer after standard adjuvant therapy – A singlearm phase II study,NCI Egypt,2014;26(4):195-202.
34. Alagizy H , Shehata M, Hashem T,et al :- Metronomic capecitabine as extended adjuvant chemotherapy in women with triple negative breast cancer.Hematology/Oncology and Stem Cell Therapy,2015.Volume 8, Issue 1, Pages 22–27
35. Cameron D, Brown J, Dent R, *et al :*-Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial.Lancet Oncol,2013, 14 (10) , pp. 933–942.