RESEARCH ARTICLE

Aromatase Inhibition and Capecitabine Combination as 1st or 2nd Line Treatment for Metastatic Breast Cancer - a Retrospective Analysis

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Abstract

Background: Preclinical studies have shown that the combination of an aromatase inhibitor (AI) and capecitabine in estrogen receptor (ER)-positive cell lines enhance antitumor efficacy. This retrospective analysis of a group of patients with metastatic breast cancer (MBC) evaluated the efficacy and safety of combined AI with capecitabine. Materials and Methods: Patients with hormone receptor-positive metastatic breast cancer treated between 1st January 2005 and 31st December 2010 with a combination of capecitabine and AI were evaluated and outcomes were compared with those of women treated with capecitabine in conventional dose or AI as a monotherapy. Results: Of 72 patients evaluated, 31 received the combination treatment, 22 AI and 19 capecitabine. The combination was used in 20 patients as first-line and 11 as second-line treatment. Mean age was 46.2 years with a range of 28-72 years. At the time of progression, 97% had a performance status of <2 and 55% had visceral disease. No significant difference was observed between the three groups according to clinical and pathological features. Mean follow up was 38 months with a range of 16-66 months. The median PFS of first-line treatment was significantly better for the combination (PFS 21 months vs 8.0 months for capecitabine and 15.0 months for AI). For second-line treatment, the PFS was longer in the combination compared with capecitabine and AI groups (18 months vs. 5.0 months vs. 11.0 months, respectively). Median 2 year and 5 year survival did not show any significant differences among combination and monotherapy groups. The most common adverse events for the combination group were grade 1 and 2 hand-foot syndrome (69%), grade 1 fatigue (64%) and grade 1 diarrhoea (29%). Three grade 3 hand-foot syndrome events were reported. Conclusions: Combination treatment with capecitabine and AI used as a first line or second line treatment was safe with much lowered toxicity. Prospective randomized clinical trials should evaluate the use of combination therapy in advanced breast cancer to confirm these findings.

Keywords: Aromatase inhibitors - capecitabine - metastatic breast cancer

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Introduction

Breast cancer is recognized as the commonest cancer in females, and the second commonest malignant tumor, after lung cancer, in overall figures worldwide (Shankar et al., 2015). Breast cancer is increasingly recognized as a heterogeneous disease exhibiting substantial differences with regard to biological behavior and requiring distinct therapeutic interventions (EBCTG, 2005). There has been a continuous decline in mortality over recent years as a direct result of improvements in early diagnosis and increased availability of more effective treatments (Winkfield et al., 2009; Cady et al., 2011). However, despite these improvements, metastatic breast cancer (MBC) remains a largely incurable disease and new treatments need to prolong survival, relieve symptoms, and delay progression. Approximately 75% of breast cancers express either or both the estrogen receptor (ER) and progesterone receptor (PgR) (Lal et al., 2005). Hormone receptor (HR)-positive and negative disease differs in terms of clinical behavior, prognosis, patterns of recurrence, and aggressiveness. Patients with HR-positive disease are likely to have more indolent disease, bone metastases, and late recurrences (Blanca et al., 1990). For most HR-positive MBC patients, endocrine therapy is the preferential initial treatment and has a positive

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Recently, a number of compounds with different mechanisms of action, low toxicity, and superior efficacy have become available for patients with HR-positive disease. Three classes of endocrine therapies are commonly used to treat HR-positive MBC: selective estrogen receptor modifiers (SERMs), such as tamoxifen, which directly bind to the ER and block its transcriptional activity; selective estrogen receptor downregulators (SERDs), such as fulvestrant, which bind to ER and induce its degradation; and aromatase inhibitors (AIs), such as letrozole, anastrozole, and exemestane, which reduce the production of estrogen via inhibition of the aromatase enzyme in peripheral tissues and within the tumor itself (Pietras et al., 2006).

Chemotherapy, whose benefits have been clearly demonstrated in multiple studies, remains the mainstay of the treatment of these patients in the neoadjuvant, adjuvant, and metastatic disease setting (Carey et al., 2007; Cleator et al., 2007). Capecitabine mimics continuous infusion of 5-FU (Van Custem et al., 2001), and the oral formulation meets with a high degree of acceptance by both patients and physicians (Finek et al., 2009). In metastatic breast cancer, the registered monotherapy dose has never been compared with lower doses in a randomized trial, but data from retrospective analyses indicate that dose reduction does not impair efficacy, and that lower doses actually have a more favorable therapeutic index than the standard dosage (Sezgin et al., 2007; Yap et al., 2007).

Protracted exposure to low doses of conventional cytotoxic drugs also offers important advantages in terms of significantly reduced toxicity (Emmeneger et al., 2007). In two small randomized trials, continuous use of low dose capecitabine (650 or 800 mg/m² b.i.d. with no drug-free breaks) proved to be just as effective in MBC patients as intermittent use of higher doses (1000 or 1250 mg/m² b.i.d. days 1-14 every 21 days) (Stockler et al., 2007; Martin et al., 2009). On the basis of this evidence, we initiated this study to investigate the tolerability, and survival in patients with hormone positive metastatic breast cancer who received 1 year of capecitabine (650 mg/m², twice every day) alone or in combination with Aromatase Inhibitors.

Preclinical studies have shown that the combination of an aromatase inhibitor (AI) and capecitabine in estrogen receptor (ER) - positive cell lines enhance antitumor efficacy. This retrospective analysis of a group of patients with metastatic breast cancer (MBC) evaluates the efficacy and safety of combined AI with capecitabine. Patients who were evaluated with a combination of capecitabine and AI were evaluated and outcomes were compared to women treated with capecitabine or AI as monotherapy.

Materials and Methods

Patient eligibility criteria

Patients with hormone receptor-positive metastatic breast cancer treated between 1st January 2005 and 31st December 2010 with a combination of capecitabine and AI were evaluated and outcomes were compared to women treated with capecitabine or AI as monotherapy.

Design of the study

This study is retrospective single institution study. Patients who received AI or capecitabine as monotherapy or in combination as first or second line therapy were divided into three group and comparative analysis was done.

Treatment plan and dose medication

The administered total dose of capecitabine was 650mg/m² BD per day as monotherapy or in combination. Capecitabine was given for 14 days and cycle was repeated after 21 days. AI used were Letrozole or Anastrazole in dose of 2.5 mg and 1 mg respectively per day. Cycles were administered on an outpatient basis. Adequate hematological and within normal range organ functions were insured prior to each cycle. Chemotherapy was discontinued in case of disease progression or major toxicities.

Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicity was required except for fatigue. If toxicities did not resolve, then a 1-week delay was allowed.

Patient assessment

Assessment of clinical benefit: A tumor response assessment was performed after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, physical and neurological examination, CT-scan of the chest, abdomen and pelvis. Criteria of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were based on the standard definitions according to RECIST 1.0 criteria, with the overall response rate, including complete response and partial response.

Assessment of toxicity

Patients were assessed for adverse events at each site with clinical and laboratory evaluations every 3 weeks. Toxicity grading was based on the common terminology criteria for adverse events.

Primary and secondary endpoints

The primary endpoints of the study were overall response and toxicity. Secondary end points were the disease-free survival and overall survival.

Statistical analysis

Overall-survival (OS) rates were calculated from the start of the oral combination of AI and capecitabine as monotherapy or in combination in ER positive metastatic breast cancer to the time of the last follow-up visit or death using the Kaplan-Meier method with SPSS version 16.0. Disease-free survival was the time elapsed from the date of initiation of oral combination of drugs to the date of first evidence of disease progression or death in the absence of disease progression. All P values were two-tailed; a value of ≤0.05 was considered significant.

Results

Of 72 patients evaluated, 31 received the combination
treatment, 22 and AI and 19 capecitabine. Combination was used in 20 patients as first-line treatment and 11 as second-line.

Distribution of patients according to treatment

|                | AI+Capecitabine | AI | Capecitabine |
|----------------|-----------------|----|--------------|
| First line     | 11              | 9  | 7            |
| Second line    | 20              | 13 | 12           |
| Total          | 31              | 22 | 19           |

Mean age was 46.2 years with a range of 28-72 years. At the time of progression, 97% had a performance status of <2 and 55% had visceral disease. No significant difference was observed between the three groups according to clinical and pathological features. Mean follow up was 38 months with a range of 16-66 months.

Patient characteristics

Seventy-two patients were recruited in the study with pathologically proven ER +ve metastatic breast cancer patients. The base line characteristics are listed with the mean age 53.1 years (range; 40-72 years). In various subgroups, mean age was 52.5 years (40-72) in AI + Capecitabine groups whereas this was 53.9 years in AI groups and 53.1 years (43-65) in Capecitabine groups respectively. The majority of cases were of ECOG performance status of ≤2. Among metastatic patients, 20.8 % were premenopausal and 71.9 % were postmenopausal. In hormone receptor status, 19.4 % had positive progesterone receptors (PR), while 31.9% patients had positive estrogen receptors (ER), and 48.6 % had positive ER and PR.

Treatment administration

A total of 212 chemotherapy cycles were administered. Patients were treated with a median number of 4 cycles of capecitabine (range 2-12 cycles). The median treatment duration of capecitabine was 12.1 weeks. The maximum treatment duration was 63 weeks.

Toxicity

The combination therapy was generally well-tolerated. Most of the adverse events were of grade 1-2. The most common grade 3-4 toxicities included hand-foot syndrome (14.3%), diarrhea (14.3%), nausea/vomiting (9.5%), mucositis (4.8%) and rash (4.8%). Grade 3 neutropenia was observed in one patient. None of the patients developed symptomatic congestive heart failure or an asymptomatic decline in LVEF to less than 15% of the lower limit of the normal range. No patient was taken off the treatment because of toxicity and there was no treatment-related death.

Table 1. Clinico-pathological and Treatment Parameters of Breast Cancer Patients

| Parameters                        | AI + Capecitabine | AI | Capecitabine |
|-----------------------------------|-------------------|----|--------------|
| Age (years)                       | 52.5              | 53.9| 53.1         |
| Range                             | 40-72             | 44-70| 43-65       |
| Menstrual status                  |                   |    |              |
| Premenopausal                     | 4(12.9%)          | 0  | 11(57.9%)    |
| Postmenopausal                    | 27(87.1%)         | 22(100%)| 8(42.1%)   |
| Family History                    |                   |    |              |
| Present                           | 2(6.5%)           | 1(4.5%)| 0            |
| Absent                            | 29(93.5%)         | 21(95.5%)| 19(100%)  |
| Histologic type                   |                   |    |              |
| Ductal                            | 29(93.5%)         | 22(100%)| 18(94.7%)  |
| Lobular                           | 2(6.5%)           | 0  | 1(5.3%)      |
| Type of Surgery                   |                   |    |              |
| Breast conservation Surgery(BCS)  | 5(16.1%)          | 3(13.6%)| 2(10.5%)   |
| Modified Radical Masteectomy(MRM) | 11(35.4%)         | 8(36.3%)| 9(47.3%)   |
| No surgery                        | 15(48.5%)         | 11(50.1%)| 8(42.1%)   |
| Adjuvant Radiotherapy             |                   |    |              |
| Yes                               | 16(51.6%)         | 11(50%)| 11(57.8%)  |
| No                                | 15(48.4%)         | 11(50%)| 11(52.6%)  |
| Metastatic disease on presentation|                   |    |              |
| Liver                             | 11(35.4%)         | 10(45.4%)| 5(26.3%)   |
| Lung                              | 10(32.2%)         | 7(31.8%)| 4(21%)     |
| Bone                              | 18(58%)           | 17(77.2%)| 13(68.4%)  |
| Brain                             | 9(29%)            | 1(4.5%)| 2(10.5%)   |
| Palliative RT                     |                   |    |              |
| Whole Brain RT                    | 7(22.5%)          | 1(4.5%)| 2(10.5%)   |
| RT to spine and pelvis            | 16(51.6%)         | 18(81.8%)| 13(68.4%)  |
| Thoracic RT                       | 2(6.4%)           | 1(4.5%)| 1(5.3%)    |
| ECOG                              | 0                 | 0  | 2(9%)       |
| 1                                 | 13(41.9%)         | 7(31.8%)| 8(42.1%)   |
| 2                                 | 18(58%)           | 11(50%)| 11(57.8%)  |
| 3                                 | 0                 | 0  | 2(9%)       |

Table 2. Complications Related to Treatment

| Toxicities                        | AI + Capecitabine | AI | Capecitabine | P value |
|-----------------------------------|-------------------|----|--------------|---------|
| Haematological toxicity           |                   |    |              |         |
| Anemia                            |                   |    |              |         |
| Grade I/II                        | 7(22.5%)          | 1(4.5%)| 4(21%)     | 0.999   |
| Grade III/IV                      | 2(6.4%)           | 0  | 1(5.2%)     |         |
| Non–hematological toxicity        |                   |    |              |         |
| Hand and Foot syndrome            |                   |    |              |         |
| Grade I/II                        | 10(32.2%)         | 5(26.3%)|           | 0.999   |
| Grade III/IV                      | 1(3.2%)           | 1(5.2%)|             |         |
| Diarrhea                          |                   |    |              |         |
| Grade I/II                        | 9(29%)            | 1(4.5%)| 4(21%)     | 0.999   |
| Grade III/IV                      | 1(3.2%)           | 1(5.2%)|             |         |
| Nausea/Vomiting                   |                   |    |              |         |
| Grade I/II                        | 9(29%)            | 1(4.5%)| 4(21%)     | 0.676   |
| Grade III/IV                      | 2(6.4%)           | 2(10.5%)|            |         |
| Fatigue                           |                   |    |              |         |
| Grade I/II                        | 15(48.3%)         | 4(18%)| 10(52.6%)  | 0.999   |
| Grade III/IV                      | 2(6.4%)           | 1(4.5%)| 2(10.5%)   |         |

Table 3. Survival Chart

|                | AI+Capecitabine | AI | Capecitabine | P value |
|----------------|-----------------|----|--------------|---------|
| Median PFS     |                 |    |              |         |
| First line     | 21 months       | 15 months| 8 months |         |
| Second line    | 18 months       | 11 months| 5 months |         |
| Median 2 years OS | 7(63.6%)     | 5(55.5%)| 1(14.2%) | 0.838   |
| Median 5 years OS | 9(45%)         | 4(30.7%)| 1(8.33%) |         |
| First line     | 2(18.1%)       | 1(11.1%)|           | 0.999   |
| Second line    | 1(5%)          | 0 |             |         |
Dose reduction was performed in 8 patients (28.57%) with 25% reduction for both drugs. Chemotherapy was interrupted for 1 week in 2 patients (9.5%). Five patients received less than 3 cycles due to rapid disease progression.

Survival
Seventy-two patients were recruited in the study between January 2005 and December 2011. Patients were followed up until May 2012. At the time of analysis, the median follow up duration was 11.0 months (Range; 1.57-35.57 months). All our patients were followed up regularly as mentioned previously in patients and methods, with no one having lost follow up in this study.

Discussion
Breast cancer is a disease with a higher incidence in haematogenous spread (Irawan et al., 2003). Patients suffering metastatic breast carcinoma express a highly variable clinical course and outcome. Intrinsic genetic heterogeneity of the primary breast tumor may have a role in this variability and could explain it in part (Chang et al., 2003). The survival of patients with metastases is variable ranging from few months to many years. It is well established that estrogen receptor (ER) status and site of presentation of metastatic disease have the greatest impact on patient survival along with additional contributions made by patient age, disease-free interval and histological grade (James et al., 2003). Capecitabine and Aromatase Inhibitors as monotherapy have shown as an important treatment option in hormone positive metastatic breast cancer in first line or second line therapy. Preclinical studies have shown that the combination of an aromatase inhibitor (AI) and capecitabine in estrogen receptor (ER) - positive cell lines enhance antitumor efficacy. This retrospective analysis of a group of patients with metastatic breast cancer (MBC) evaluates the efficacy and safety of combined AI with capecitabine.

Currently, AIs are commonly used as a first line treatment for postmenopausal women with metastatic hormone receptor-positive breast cancer. This is based on the results of several Phase III trials that demonstrated superiority of AIs compared to tamoxifen with regards to response rate, median time to progression, and clinical benefit rate (Nabholtz et al., 2000; Bonneterre et al., 2001; Mouridsen, 2004). The largest trial in this setting enrolled 916 postmenopausal women and randomized patients to receive either tamoxifen or letrozole. Macedo et al., 2008 demonstrated a significant improvement in time to progression with letrozole compared to tamoxifen (42 versus vs 23 weeks, hazard ratio [HR] 0.70, P=0.0001).

There are several ongoing studies that include phase III trials which explore the addition of capecitabine to standard adjuvant chemotherapy or through introduction of maintenance therapy (CIBOMA, 2005)). Capecitabine is an oral fluoropyrimidine carbamate that acts as a 5-fluorouracil (5-FU) prodrug and mimics continuous infusion of 5-FU (Van Cutsem et al., 2001). Patients often prefer the convenience of an oral treatment to intravenous chemotherapy (Finkel et al., 2009; Joensuu et al., 2012).

In the past few years several studies have emphasized the role of metronomic chemotherapy to be used as extended adjuvant chemotherapy (Penel et al., 2012)). In a phase II study by Shawky and Galal, extended adjuvant capecitabine treatment phase did not appreciably increase the incidence of hematologic and non-hematologic toxicity compared with previous reports administering extended adjuvant capecitabine to MBC patients (Heitz et al., 2008; Ezz El-Arab et al., 2012; Fedele et al., 2012).

Patients of metastatic breast cancer were selected for analysis and out of 72 patients evaluated, 31 received the combination treatment, 22 AI and 19 capecitabine. Combination was used in 20 patients as first-line treatment and 11 as second-line. No significant difference was observed between the three groups according to clinical and pathological features. Mean age was 46.2 years with a range of 28-72 years. The majority of cases were of ECOG performance status of ≤2. Among metastatic patients, 20.8 % were premenopausal and 71.9 % were postmenopausal. Family history was present in 3(4.16%) patients. In hormone receptor status, 19.4 % had positive progesterone receptors (PR), while 31.9 % had positive estrogen receptors (ER), and 48.6 % had positive ER and PR. Mean follow up was 38 months with a range of 16-66 months.

The most common adverse event for the combination group were grade 1 and 2 hand-foot syndrome (69%), grade 1 fatigue (64%) and grade 1 diarrhea (29%). Three grade 3 hand-foot syndrome events were reported. In a study by Shawky and Galal, 2014, no Grade 3-4 hematologic toxicity was recorded. Hand-foot syndrome (HFS), a frequent side effect of capecitabine (Xeloda), was the most common treatment-related adverse event, occurring in 15.8% (3/19). The majority of HFS was mild to moderate. There was only 1 case (5.26%) of Grade 3/4 HFS. Diarrhea was experienced by 2 patients (10.5%) with only 1 patient (5.3%) suffering from grade 3 toxicity. Other grade 1 or 2 non-hematologic toxicities observed were nausea/vomiting in 2 patients (10.5%) and grade 1 fatigue in 1 patient (5.3%). Only 1 patient required hospitalization, because of grade 3 diarrhea. All patients received full doses of capecitabine throughout the study. Dose reduction was not required in any of our patients. Interruption of treatment was decided and performed for 1 week in only 2 patients because of Grade 3 diarrhea (1 patient) and Grade 3/4 hand-foot syndrome (1 patient). Most of hematologic and non-hematologic toxicities during the extended adjuvant capecitabine treatment phase were better than those of other previous reports (Heitz et al., 2008; Ezz El-Arab et al., 2012; Fedele et al., 2012).

Two phase II trials had studied the toxicity profile of metronomic capecitabine in metastatic breast cancer (MBC) patients. Ezz El-Arab et al. had studied the clinical efficacy and tolerability of low dose, capecitabine (500 mg twice daily) together with oral cyclophosphamide (CTX) (at dose of 50 mg once daily) in 60 patients with metastatic breast cancer. The overall regimen was well tolerated. Myelosuppression, a well-documented side effect of therapy in particular leucopenia (Grades 1 and 2) was observed in (17%) patients. Palmar-plantar erythrodysesthesia, the most frequently reported non-
hematologic adverse events, were also mild to moderate (Grades 1 and 2 in 36.7% of cases), and could be readily controlled with the administration of standard medications. Also in our study hand-foot syndrome, was the most common treatment-related adverse event, occurring in 15.8% (3/19) of patients, with only 1 case (5.3%) of Grade 3/4 while in Ezz El-Arab et al. study no grade 3 or 4 toxicity was recorded. The use of lower doses in study by Ezz El-Arab compared to those used in our study could explain the absence of grade 3 or 4 toxicities in their study. Vomiting in Ezz El-Arab et al study was much higher (28.3%) in comparison to that (10.5%) in our study; this may be due to the effect of CTX in their study. Diarrhea in our study was lower (10.5%) in comparison to that (20%) in the study by Ezz El-Arab et al. However, in our study only 1 patient (5.3%) suffered from grade 3 diarrhea, while in Ezz El-Arab et al study no grade 3 or 4 toxicity was recorded. Again this could be explained by the use of lower doses in Ezz El-Arab et al. study to those used in our study. In Ezz El-Arab et al. study Grade 3 elevation of serum transaminases was reported in 8% of patients. In our study no hepatic toxicity occurred. This difference could be explained by the addition of CTX to Xeloda in Ezz El-Arab et al. study as well as their study was conducted in metastatic patients including those with liver metastasis and the patients were also heavily pretreated. (Ezz El-Arab et al., 2012)

In another report published by Fedele et al evaluating efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer, 60 patients received continuous metronomic capecitabine monotherapy (1500 mg once a day). Hematologic toxicity was infrequent and mild. Hand foot syndrome (10%) and diarrhea (7%) were the most common adverse effects, and vomiting occurred in (2%). There were only three cases of grade 3 toxicity, all involving hand-foot syndrome (Fedele et al., 2012).

The median PFS of first-line treatment was significantly better for the combination (PFS 21 month’s vs.8.0 months for capecitabine and 15.0 months for AI). For second-line treatment, the PFS was lower in the combination compared with capecitabine and AI (PFS 18 months vs. 5.0 months vs. 11.0 months, respectively). For the entire cohort, 2 years, Median OS of 1st line was 63.6% in AI + Capecitabine group followed by 55.5% in AI group whereas in 2nd line treatment, 2 years median OS was 45% in combination group. 5 years OS was seen in 2 patients as 1st line and in 1 patient as 2nd line in combination group. In AI group, one patient survived for 5 years.

In conclusion, combination treatment with capecitabine and AI used as a first line or second line treatment was safe with much less toxicity. Prospective randomized clinical trials should evaluate the use of combination therapy in advanced breast cancer to confirm these findings.

References

Blanco G, Holli K, Heikkinen M, Kallioniemi OP, Taskinen P (1990). Prognostic factors in recurrent breast cancer: relationships to site of recurrence, disease-free interval, female sex steroid receptors, ploidy and histological malignancy grading. *Br J Cancer*, **62**, 142-46.

Bonneteer J, Buzdar A, Nabholz JM, et al (2001). Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer*, **92**, 2247-58.

Cady B, Michaelson JS, Chung MA (2011). The „tipping point” for breast cancer mortality decline has resulted from size reductions due to mammographic screening. *Ann Surg Oncol*, **18**, 903-6.

Carey LA, Dees EC, Sawyer L, et al (2007). The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res*, **13**, 2329-34.

Chang J, Clark G M, Allred D C, et al (2003). Survival of patients with metastatic breast carcinoma. *Cancer*, **97**, 545-53.

Cleator S, Heller W, Coombes RC (2007). Triple-negative breast cancer: therapeutic options. *Lancet Oncol*, **8**, 235-44.

Early Breast Cancer Trialists’ Collaborative Group (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, **365**, 1687-717.

Emmenegger U, Kerbel RS (2007). Five years of clinical experience with metronomic chemotherapy: achievements and perspectives. *Onkologie*, **30**, 606-8.

Ezz El-Arab L, Swellamb M, El Mahdy M (2012). Metronomic chemotherapy in metastatic breast cancer: impact on VEGF. *J Egypt Natl Canc Inst*, **24**, 15-22.

Fedele P, Marino A, Orlando L, et al (2012). Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. *Eur J Cancer*, **48**, 24-9.

Finek J, Holubec L, Svoboda T, et al (2009). A phase II trial of oral vinorelbine and capecitabine in anthracycline pretreated patients with metastatic breast cancer. *Anticancer Res*, **29**, 667-70.

Group SBCR: maintenance treatment with capecitabine versus observation in breast cancer patients (CIBOMA), 2005.

Heitz F, Harter P, Traut A, et al (2008). Cerebral metastases (CM) in breast cancer (BC) with focus on triple-negative tumors. *J Clin Oncol*, **26**.

Irawan C, Hukom R, Prayojo N (2003). Factors associated with bone metastasis in breast cancer: a preliminary study in an indonesian population, acta med Indones- Indones. *J Internal Med*, **40**, 178-80.

James J, Evans AJ, Pinder SE, et al (2003). Bone metastases from breast carcinoma: histopathological - radiological correlations and prognostic features. *Br J Cancer*, **18**, 660-5.

Joensuu H, Gligorov J (2012). Adjuvant treatments for triple receptor positive advanced breast carcinoma. *Clin Cancer Res*, **18**, 679-88.

Lai P, Tan LK, Chen B (2005). Correlation of HER-2 status with estrogen and progesterone receptors and histologic features in 3,655 invasive breast carcinomas. *Am J Clin Pathol*, **123**, 541-46.

Macedo LF, Sabnis G, Brodie A (2008). Preclinical modeling of endocrine response and resistance: focus on aromatase inhibitors. *Cancer*, **112**, 679-88.

Martin M, Calvo L, Martinez N, et al (2009). Randomized, phase II trial comparing continuous versus intermittent capecitabine monotherapy for metastatic breast cancer (MBC), ASCO annual meeting proceedings part I. *J Clin Oncol*, **27**, 1086.

Mouridsen HT (2004). Aromatase inhibitors in advanced breast cancer. *Semin Oncol*, **31**, 3-8.

Nabholz JM, Buzdar A, Pollak M, et al (2000). Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *Arimidex Study*.
| Group. J Clin Oncol, 18, 3758-67. |
|---|
| Pietras RJ (2006). Biologic basis of sequential and combination therapies for hormone-responsive breast cancer. Oncologist, 11, 704-17. |
| Sezgin C, Kurt E, Evrensel T, et al (2007). Efficacy of lower dose capecitabine in patients with metastatic breast cancer and factors influencing therapeutic response and outcome. South Med J, 100, 27-32. |
| Shankar A, Rath GK, Roy S, et al (2015). Level of awareness of cervical and breast cancer risk factors and safe practices among college teachers of different states in India: do awareness programmes have an impact on adoption of safe practices? Asian Pac J Cancer Prev, 16, 927-32. |
| Shawky H, Galal S (2014). Preliminary results of capecitabine metronomic chemotherapy in operable triple-negative breast cancer after standard adjuvant therapy - A single-arm phase II study. J Egypt Natl Canc Inst, 26, 195-202. |
| Stockler M, Sourjina T, Grimison P, et al (2007). A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first line chemotherapy for advanced breast cancer. ASCO Annual Meeting Proceedings Part I. J Clin Oncol, 25, 1031. |
| Van Cutsem E, Twelves C, Cassidy J, et al (2001). Xeloda colorectal cancer study group. oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol, 19, 4097-106. |
| Winkfield KM, Harris JR (2009). Effective local therapy and long-term survival in breast cancer. Oncology (Williston Park), 23, 669-75. |
| Yap YS, Kendall A, Walsh G, Banerji U, Johnston SRD, Smith IE, et al (2007). Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer - How low can you go? Breast, 16, 420-4. |