Full Length Article

Preliminary results of capecitabine metronomic chemotherapy in operable triple-negative breast cancer after standard adjuvant therapy – A single-arm phase II study

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KEYWORDS
Triple-negative breast cancer; Capecitabine metronomic therapy

Abstract Purpose: The aim of this study is to investigate efficacy and toxicity of 1 year of capecitabine metronomic therapy preceded by standard adjuvant chemotherapy in triple-negative breast cancer (TNBC) patients.

Methods: Between June 2010 and February 2012, 19 women with pathologically proven operable TNBC, who had received standard adjuvant chemotherapy before were enrolled. Patients received 1 year of oral capecitabine metronomic therapy (650 mg/m², twice every day), after standard adjuvant chemotherapy and radiotherapy if indicated. The primary endpoints of this study were disease-free survival rates (DFS) and safety profile. Secondary end point was overall survival (OS).

Results: The maximal follow-up was 46.6 months with a median of 30.1 months ± 11.525 (95% CI; 28.5–33.5 months). The median DFS was 41.7 months ± 2.7 (95% CI; 36.5–46.9). No one developed locoregional recurrence. The actuarial rate of DFS was 88.8% and 82.05% at 2 and 3 years, respectively. At the time of the analyses, no patients had died and the median OS was not reached.

Treatment-related adverse events were manageable with only 1 patient (5.3%) suffering from Grade 3/4 hand-foot syndrome and another 1 patient (5.3%) suffering from Grade 3 diarrhea. No Grade 3/4 hematologic toxicity was recorded. All patients received full doses of capecitabine throughout the study and dose reduction was not required in any of our patients.

Conclusion: One year of capecitabine metronomic therapy preceded by standard adjuvant chemotherapy, is active and well-tolerated in TNBC patients previously treated with standard adjuvant chemotherapy.

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Introduction

Breast cancer (BC) is increasingly recognized as a heterogeneous disease exhibiting substantial differences with regard to biological behavior and requiring distinct therapeutic interventions. Steroid hormone receptors (HR) such as estrogen receptor (ER) and progesterone receptor (PgR) in concert with the oncogene ErbB-2/human epidermal growth factor receptor 2 (HER-2) are critical determinants of these BC subtypes. While HR are thought to mirror a good prognosis [1], expression of HER-2 has long been understood as an unfavorable prognostic feature [2]. However, since the introduction of trastuzumab as a potent therapeutic approach in HER-2 positive BC, HER-2 expression is perceived as a favorable predictive rather than negative prognostic factor [3,4].

Overall, the prevalence of TNBC in large unselected breast cancer patient cohorts is 11–20% [5,6], whereas in selected cohorts of patients with advanced BC or patients of African-American ethnicity, TNBC may be diagnosed among as many as 23–28% of patients [7,8].

Patients with TNBC have a grim prognosis with a short PFS and OS [9,10]. Although several studies are defining the role of biological agents in the management of TNBC [11], 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 [12,13].

There is no universally accepted standard chemotherapy regimen for adjuvant treatment of TNBC, and classical regimens, are currently reasonable choices. Studies that address novel agents, platinum compounds and different methods of drug administration are ongoing for the adjuvant treatment of TNBC, and the results are eagerly awaited [14].

Capecitabine mimics continuous infusion of 5-FU [15], and the oral formulation meets with a high degree of acceptance by both patients and physicians [16]. 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 [17], and that lower doses actually have a more favorable therapeutic index than the standard dosage [18,19].

Metronomic regimens involve the frequent (daily, or several times a week, or weekly) or continuous administration of chemotherapy agents at low doses, without lengthy drug-free breaks. This approach is known to enhance the antiangiogenic activity of these drugs [20,21]. Protracted exposure to low doses of conventional cytotoxic drugs also offers important advantages in terms of significantly reduced toxicity [22]. Its pharmacokinetic characteristics and low toxicity profile make capecitabine an ideal drug for metronomic administration [23]. 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) [24,25].

On the basis of this evidence, we initiated this study to investigate the tolerability, and survival in patients with operable TNBC who received 1 year of metronomic capecitabine (650 mg/m², twice every day) preceded by standard adjuvant therapy.

Materials and methods

Patient eligibility criteria

Between June 2010 and February 2012, 19 women with pathologically proven hormone receptor-negative, HER2-negative (triple receptor negative) breast cancer, were enrolled in Clinical Oncology Department, Tanta University Hospital. Patients were followed up until July 2014. At the time of analysis, the median follow up duration was 30.1 months (Range: 28.5–46.6 months).

All patients had operable, node-positive breast cancer (or node negative with tumor diameter ≥1 cm). Patients fulfilled the following criteria: – age between 18 and 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2, adequate bone marrow reserve (WBC count ≥3.5 × 10⁹/L, ANC count ≥1.5 × 10⁹/L, platelets ≥100 × 10⁹/L, and hemoglobin ≥10 g/dL), adequate renal function (measured creatinine clearance ≥60 mL/min) and adequate liver function (transaminases less than 2 × upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Patients were ineligible for this study if they had metastases to distant sites, or patients who were pregnant or have dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent were excluded from this study. Also, patients suffering from secondary malignancy or concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, and clinically significant cardiac disease) were not eligible.

Design of the study

This study is a prospective single-arm phase II single institution study. The Ethics Committee in Faculty of Medicine, Tanta University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

Treatment plan and dose medication

Eligible patients received standard adjuvant chemotherapy that included anthracycline, either, in the form of FAC, FEC, or sequential FEC with taxanes followed by radiotherapy if indicated. After confirmation of immunohistochemistry status, patients received 1 year of oral capecitabine (Xeloda) metronomic therapy (650 mg/m², twice every day).

Oral capecitabine (Xeloda) metronomic therapy is discontinued in case of disease progression or major toxicities. Chemotherapy is administered on an outpatient basis.

Adequate hematological and within normal range organ functions were insured every month. Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicities was required except for alopecia and fatigue. If toxicities did not resolve, then a 1–2 week delay was allowed.

Patient assessment

Pre- and on-treatment monitoring consisted of medical history, physical and local examination, mammography, chest X-ray,
abdomen and pelvis ultrasonography and/or CT scans, and bone marrow reserve, renal function and liver function measurement. Toxicity grading was based on the common terminology criteria for adverse event (NCI-CTC, version 3.0) [26].

Primary and secondary endpoints

The primary endpoints of this study were disease-free survival rates and safety profile. Secondary end point was overall survival.

Statistical analysis

Overall-survival (OS) rates were calculated from the date of start of treatment to the time of the last follow-up visit or death using the Kaplan–Meier method [27] with SPSS [Statistical package] (version 12.0). Disease-free survival (DFS) was the time elapsed from the date of initiation of treatment to the date of first evidence of disease relapse or death in the absence of disease relapse. Kaplan–Meier method [27] is used for estimating survival. 95% confidence intervals (95% CIs) were calculated with the exact method.

Results

Patient characteristics

Nineteen patients with pathologically proven operable, node-positive (or node negative with tumor diameter \( \geq 1 \) cm), hormone receptor-negative, HER2-negative (triple receptor negative) breast cancer were enrolled in this study. The baseline demographic and clinical characteristics of all enrolled patients are listed in table 1.

The median age at disease diagnosis was 50.9 years (range 29–70 years), in which 12 (63.2%) patients were postmenopausal and 7 (36.8%) patients were premenopausal. The majority of patients had invasive ductal carcinoma (89.5%) and grade III disease (68.4%). T2 disease constituted 57.8% of all patients at initial presentation prior to any treatment. Most of the patients (94.7%) had ECOG performance status score of \( \leq 1 \). Eleven patients (57.9%) underwent mastectomy for their primary tumor, and 8 patients (42.1%) underwent a segmental resection. All patients received adjuvant combination chemotherapy and 10 (52.6%) patients received adjuvant radiation therapy following surgery and combination chemotherapy. All patients had triple receptor negative breast cancer (TNBC).

Treatment administration

All patients received 1 year of oral capecitabine (Xeloda) metronomic therapy (650 mg/m², twice every day). The last patient finished capecitabine metronomic therapy in August 2013. No dose reduction was recorded and only 2 patients had a dose delay of 1 week because of Grade 3 diarrhea (1 patient) and Grade 3/4 hand-foot syndrome (1 patient).

Toxicity

To date, the main forms of adverse reactions to this regimen observed in the 19 assessable patients are listed in table 2. Most of hematologic and non-hematological toxicities were mild and manageable. No Grade 3/4 hematologic toxicity was recorded.

Hand-foot syndrome, a frequent side effect of capecitabine (Xeloda), was the most common treatment-related adverse event, occurring in 15.8% (3/19) of patients. Two (10.5%) of them were of Grade 1/2 hand-foot syndrome while, only 1 case (5.3%) had Grade 3/4 hand-foot syndrome, which was rapidly resolved to grade 0/1 with rest and symptomatic treatment. Diarrhea was experienced by 2 patients (10.5%) with one of them (5.3%) suffering from grade 3 toxicity. Other grade 1/2 non-hematologic toxicities observed were nausea/vomiting in 2 patients (10.5%) and fatigue in 1 patient (5.3%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>Median</td>
<td>50.9 years</td>
</tr>
<tr>
<td>Range</td>
<td>29–70</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>+ ve</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>− ve</td>
<td>17 (89.5%)</td>
</tr>
<tr>
<td>Tumor status</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>T2</td>
<td>11 (57.8%)</td>
</tr>
<tr>
<td>T3</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>7 (36.8%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>12 (63.2%)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>G2</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>G3</td>
<td>13 (68.4%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Invasive duct carcinoma (IDC)</td>
<td>17 (89.5%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Negative</td>
<td>13 (68.4%)</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
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<tr>
<td>N0</td>
<td>9 (47.4%)</td>
</tr>
<tr>
<td>N1</td>
<td>6 (31.5%)</td>
</tr>
<tr>
<td>N2</td>
<td>4 (21.1%)</td>
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<tr>
<td>Adjuvant radiation therapy (Rth)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (52.6%)</td>
</tr>
<tr>
<td>No</td>
<td>9 (47.4%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Breast conserving surgery (BCS)</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Modified radical mastectomy (MRM)</td>
<td>11 (57.9%)</td>
</tr>
<tr>
<td>Type of adjuvant chemotherapy</td>
<td></td>
</tr>
<tr>
<td>FAC</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>FEC</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td>Sequential FEC with taxanes</td>
<td>10 (52.6%)</td>
</tr>
<tr>
<td>ECOG</td>
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</tr>
<tr>
<td>0</td>
<td>15 (78.9)</td>
</tr>
<tr>
<td>1</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>2</td>
<td>1 (5.3)</td>
</tr>
</tbody>
</table>

Table 1 Patients’ and tumor characteristics as well as initial treatment modality of the 19 TNBC patients managed by 1 year capecitabine metronomic therapy.
Only 1 patient required hospitalization, because of grade 3 diarrhea. All patients received full doses of capecitabine throughout the study and dose reduction was not required in any of our patients. However, only 2 patients had a dose delay of 1 week because of Grade 3 diarrhea (1 patient) and Grade 3/4 hand-foot syndrome (1 patient).

**Survival**

All our patients were followed up regularly as mentioned previously in patients and methods, with no one lost to follow up in this study. The maximal follow-up was 46.6 months with a median of 30.1 months (Range; 28.5–46.6 months).

At the time of this analysis, 16 of 19 patients had not yet experienced either intra- or extracranial distant metastases. In 3 patients, distant metastases were recorded: 2 patients for extracranial-only visceral disease progression and 1 patient for distant metastases both at intra- and extracranial visceral sites. No one developed locoregional recurrence. Among our 19 TNBC patients, the actuarial rate of DFS was 88.8% and 82.1% at 2 and 3 years, respectively, (Fig. 1). At the time of the analyses, no patients had died.

**Discussion**

Triple negative breast cancer (TNBC) is an aggressive disease characterized by a lack of expression of both estrogen receptors, and progesterone receptors, as well as human epidermal growth factor receptor 2 (HER2) [9]. Several studies have shown that TNBC is associated with an increased response rate to systemic chemotherapy [13,28,29], and improvements in chemotherapy are likely to preferentially benefit this subtype of breast carcinoma because of rapid proliferation rates and defects in DNA repair. However, there is no preferred standard form of chemotherapy for TNBC [30].

Other strategies have been adopted to improve the clinical outcome of patients with TNBC. Bevacizumab [anti-vascular endothelial growth factor (VEGF) monoclonal antibody] has been evaluated in patients with TNBC [31–34]. Antiangiogenic therapy has been studied in large phase III clinical trials as first-line [35,36] and second-line [37] treatment of metastatic breast cancer. Adjuvant bevacizumab in combination with taxanes is being prospectively investigated in TNBC in the BEATRICE trial with the estimated study completion date being January 2015 [14].

Epidermal growth factor receptor (EGFR)-targeted agents are being studied in TNBC given a high-level EGFR of expression in some of these cancers [38,39]. EGFR inhibitors have demonstrated low efficacy as single agents in TNBC, but in combination may improve the efficacy of other agents, such as taxanes or platinums. However, these agents have a limited role and could not be used widely for TNBC patients in our country because of limited resources.

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 [40–42].

Capecitabine is an oral fluoropyrimidine carbamate that acts as a 5-fluorouracil (5-FU) prodrug and mimics continuous infusion of 5-FU [15]. Patients often prefer the convenience of an oral treatment to intravenous chemotherapy [14,16]. Capecitabine has been investigated in the adjuvant setting for the prevention of breast cancer recurrence [43,44].

In the past few years several studies have emphasized the role of metronomic chemotherapy to be used as extended adjuvant chemotherapy [45]. Some metronomic regimens can have surprisingly potent antitumor effects in preclinical models compared with respective maximum tolerated dose (MTD) regimens, despite being less toxic [46].

Because of the high variability of the extended adjuvant capecitabine treatment dose ranging from a tenth to a third of the maximum tolerated dose (MTD) we designed this phase II trial to investigate the efficacy and tolerability of 1 year of capecitabine (Xeloda) metronomic therapy at a dose of 650 mg/m², twice every day as extended adjuvant in newly diagnosed TNBC who received standard adjuvant chemotherapy followed by radiotherapy if indicated. The primary endpoints of this study were DFS and safety profile. Secondary end point was OS.

To our knowledge, this is the first prospective study to assess 1 year metronomic capecitabine in patients with operable TNBC in our country. Our study confirms the overall acceptable tolerability of extended adjuvant capecitabine. The 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 [48–50].
To date, most of the adverse reactions to this regimen observed in our 19 assessable patients were mild and manageable. 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) of our patients. 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 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 [48,50]. Two phase II trials had studied the toxicity profile of metronomic capecitabine in metastatic breast cancer (MBC) patients. Ezz El-Arab et al. [48] 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 erythrodythesia, 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. [48] study no grade 3 or 4 toxicity was recorded. The use of lower doses in Ezz El-Arab et al. [48] study 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. [48] 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. [48]. However, in our study only 1 patient (5.3%) suffered from grade 3 diarrhea, while in Ezz El-Arab et al. [48] 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. [48] study to those used in our study. In Ezz El-Arab et al. [48] study Grade 3 elevation of serum transaminases was reported in 8% of patients [48]. 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. [48] study as well as their study was conducted in metastatic patients including those with liver metastasis and the patients were also heavily pretreated.

In another report published by Fedele et al. [50] 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 [50]. These results were comparable to our results with no hepatic toxicity recorded.

Evaluating toxicity resulting from exposure to capecitabine as a maintenance therapy after standard adjuvant therapy remains a concern. Two phase III ongoing studies are evaluating extended adjuvant capecitabine treatment after standard adjuvant therapy (CIBOMA and SYSCBS-001) [28]. In CIBOMA 2004-01/GEICAM 2003-11 a multicenter, open-label, randomized phase III trial evaluated the efficacy of extended adjuvant capecitabine treatment, in operable TNBC. Patients with operable, TNBC who have received standard adjuvant chemotherapy were eligible. They were randomized to receive 8 cycles of Capecitabine (1000 mg/m2 bid, d1–14 q21d) (Arm A) or observation (Arm B) [40].

SYSCBS-001 is an open-label, randomized phase III trial, evaluating the efficacy of extended adjuvant capecitabine treatment in TNBC. Patients with early TNBC were randomized to treatment with standard adjuvant chemotherapy followed by observation or to standard adjuvant chemotherapy followed by 1 year of extended adjuvant capecitabine treatment 650 mg/m2 twice every day [42].

Our study differs from the previously mentioned trials in being a prospective one arm phase II study that included only 19 patients with operable, TNBC. However, in this study like both CIBOMA and SYSCBS-001, patients with T4 and N3 were excluded and all patients received 6 cycles of standard adjuvant chemotherapy before extended adjuvant capecitabine treatment.

The dose of capecitabine differs between the CIBOMA trial [40] and both the SYSCBS-001 trial and our study. In the CIBOMA trial patients received a standard dose (not the metronomic dose) of capecitabine 1000 mg/m2 bid, d1–14 q21d for 8 cycles, while in the SYSCBS-001 trial [42] and our study patients received metronomic capecitabine 650 mg/m2 twice every day for one year. We choose in this study the lower SYSCBS-001 trial [42] doses as they are expected to be associated with more tolerability, lower costs, and lower burden on our limited national resources.

Unfortunately, there are no published data about the toxicity profile in the SYSCBS-001 trial till now [42].

In comparison to the CIBOMA safety profile, most of the adverse effects in our study are lower, this is due to the lower dose of capecitabine we used. The first safety data from the randomized phase III (CIBOMA 2004-01/GEICAM 2003-11) trial were published by Lluch et al. in San Antonio cancer symposium 2010 revealing that more than 75% of patients were able to continue their treatment as planned with approximately 15% of patients discontinuing due to toxicity or withdrawal. Grade 3 or 4 adverse effects were higher in extended adjuvant capecitabine treatment, hand foot syndrome 17.4%, diarrhea 2.9%, vomiting 1.0%, and elevated bilirubin 1.0% [41]. This preliminary safety analysis on 405 patients reported 7 serious adverse events considered possibly related to capecitabine (hospitalization for grade 2–4 diarrhea in 3 patients; grade 2 thoracic pain, grade 2 arrhythmia, coronary vasospasm and chest pain in 1 patient each) [14]. However, we are waiting for the final results of both CIBOMA and SYSCBS-001 to compare our results with their results.
TNBC accounts for a disproportionate number of BC deaths; the majority of studies indicate a negative impact of a TN (on the basis of data of thousands of patients) phenotype on patient prognosis [7,8,13,28,51]. Importantly, the prognostic effect of TNBC is independent of poor grade, nodal status, tumor size and treatment [51,52]. At the time of this analysis, in our study, not one of our patients had died. The median duration of follow-up was 30.1 ± 11.5 months, (range 10.1–46.6 months).

TNBC has been investigated by a number of investigators as regards the risk of local relapse after conservative surgery and radiation. In a study by Haffty et al. [53] reported that there is no evidence that these patients are at a higher risk of local relapse after conservative surgery and radiation [53]. Our study confirms the overall good efficacy of extended adjuvant capecitabine, as in our study, none of our patients developed locoregional relapse whether treated by conservative surgery and radiation or MRM with or without adjuvant radiation therapy.

The aggressiveness of TNBC is further indicated by the fact that (i) the peak risk of recurrence occurs within the first 3 years after the initial treatment of the disease with the majority of deaths occurring in the first 5 years [54] and (ii) after diagnosis of metastatic disease, a significantly shorter survival was observed in TNBC [28,55,56].

Our results about the timing of recurrence are comparable to the data of previous investigators [54], the relapse events in our study had occurred during the first 3 years after diagnosis. However, our results were promising as only 3 relapse events have occurred 3/19 (15.8%), with no one developing locoregional recurrence, so metronomic capecitabine might be associated with decreased incidence of relapse in first 3 years in patients with TNBC. However, these results are preliminary due to small sample size as well as short follow up period. Thus, a larger number of patients and longer follow-up period are necessary.

TNBC has a different pattern of relapse [32]. Several studies have supported a significantly increased rate of visceral versus bone metastasis [32,57] among patients with TNBC compared with non-TNBC. In the largest report to date, data on 12 858 patients indicate an increased risk for the lung [odds ratio (OR) 2.27] and brain (OR 5.32) metastasis as the first site of recurrence and a lower risk of bone recurrence (OR 0.23) in patients with TNBC [6]. Also, patients with TNBC compared with other subtypes reportedly experienced an increased risk of central nervous system metastases (CM) of 6–46% of those experiencing metastatic spread of the disease [49,58,55]. Similarly, in a single-institution study among 3193 patients, a significantly elevated risk of CM among patients with TNBC and HER-2-positive BC compared with other phenotypes has been reported (HR 4.5 and 4.9 for TNBC and HER-2+, respectively) [49].

In our study 1 patient (5.3%) from 3 patients (15.8%) who had developed distant metastases, had intra-cranial disease metastases. Comparison between our results and the results of other trials is difficult, because we couldn’t have a firm conclusion about the pattern of relapse, due to the small number of patients and a short follow up period.

Several studies have shown that women with TNBC are at a higher likelihood of relapse and have an associated poorer prognosis compared with women with other subtypes of breast cancer [13,53]. Survival results in our study are encouraging. In our series, only 3 relapse events have occurred (3/19 (15.8%)), without development of any locoregional recurrence. At the time of analyses, no patients had died and median OS was not reached. Indeed, the actuarial rate of DFS of 88.8% and 82.1% at 2 and 3 years, respectively, compares favorably with the other previous reported data published in Dawood et al. [58] study. Dawood et al. [58], studied 679 patients with non-metastatic TNBC, with median follow-up among all patients of 26.9 months (range 1.1–321.3 months), two hundred (29.5%) patients have experienced disease recurrence, and DFS at 2 and 5 years was 69.2% and 59.6%, respectively. At the time of this analysis, 153 (22.5%) patients had died and OS at 2 and 5 years was 85.9% and 64.1%, respectively [58]. So the incidence of both local and distant relapses in our study was lower in comparison to the previously published data of Dawood et al. [58] study, but larger samples and longer follow-up are required for better and mature results. However, our preliminary findings suggest that metronomic capecitabine is an active extended adjuvant treatment of patients with TNBC.

Unfortunately there are no published data about the survival results of both CIBOMA and SYSCBS-001trials till now, because they are still ongoing [40].

Conclusion

To our knowledge, this is the first report of results of 1 year extended adjuvant capecitabine therapy in the treatment of TNBC in our country. The preliminary results of our study demonstrated that, extended adjuvant capecitabine treatment, for patients with TNBC is a promising regimen in decreasing the incidence of both locoregional recurrence and distant relapse in the first 3 years, with acceptable toxicity profile. Thus, we propose that extended adjuvant capecitabine treatment is an alternative approach with tolerable toxicities for patients with TNBC, nevertheless, the challenge remains to improve clinical outcomes further. To confirm this, a multicenter, meta-analysis and a randomized trial with a large number of patients are required in the near future.

Conflict of interest

We have no conflict of interest to declare.

References


Capecitabine metronomic chemotherapy


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


University SY-s: efficacy of capecitabine metronomic chemotherapy to triple-negative breast cancer (SYSCBS-001), 2010.


