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ORIGINAL ARTICLE

Metronomic Capecitabine in Metastatic Triple negative breast cancer.

Asima Luqman[1], Sarah Khan[2]

ABSTRACT… Objective: To evaluate the efficacy and safety of metronomic capecitabine in patients with metastatic TNBC (mTNBC), with progression free survival (PFS) as primary end point and toxicity profile as secondary endpoint. **Study Design:** Retrospective study. **Setting:** Department of Radiotherapy, Quaid e Azam Medical College, Bahawalpur, Pakistan. **Period:** 1st January 2022 to 30th October 2025. **Methods:** The study included patients with mTNBC of any age who were metastatic at presentation. All patients received first-line chemotherapy, or subsequently went on to receive the second-line chemotherapy. Capecitabine at a dose of 500 mg twice daily was administered to patients with stable disease after initial chemotherapy. Patients were asked to follow up every 4 weeks and thorough clinical examination was performed at each follow up. **Results:** Out of 643 breast cancer patients, 117 (18.2%) had stage IV disease, with 47 (40.1%) having mTNBC. The median age was 44 years. There were 33 (70.2%) patients who achieved stable disease and started metronomic capecitabine following initial chemotherapy. Among these 33 patients, 24 (72.7%) had stable disease while remaining 9 (27.3%) experienced disease progression. The most common toxicities were mild nausea and vomiting, noted in 9 (27.2%), grade 1 diarrhea 4 (12%), grade 1 mucositis 3 (9.1%), and grade 1 myelosuppression 4 (12.4%). **Conclusion:** Metronomic capecitabine was an effective and well-tolerated treatment option for patients with mTNBC, particularly in the short term.

Key words: Capecitabine, Nausea, Patient, Toxicity, Vomiting.

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INTRODUCTION

Triple-negative breast cancer (TNBC) is recognized as one of the most aggressive and challenging subtypes of breast cancer. Unlike other forms of breast cancer, TNBC is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) expression.[1,2] This lack of hormone receptors and HER2 expression means that TNBC does not respond to hormonal therapies or therapies targeting HER2, such as trastuzumab, which are commonly effective in other breast cancer subtypes. The result is a distinct clinical entity with unique biological features, often presenting with higher tumor grade, increased mitotic index, and a tendency for rapid proliferation and growth.[3] The clinical behavior of TNBC is typically aggressive, with a higher probability of early recurrence, particularly in the first three to five years following initial diagnosis.[3] Women with TNBC are also more likely to experience visceral metastases, including to the lungs, liver, and brain, as compared to other subtypes that may more commonly involve bone. The incidence of TNBC ranges from 15% to 20% of all invasive breast cancers, representing a significant proportion of cases worldwide.[4] The burden is especially high in younger women and certain ethnic populations, including African and South Asian women, where TNBC is found at higher frequencies and is often diagnosed at more advanced stages.[4]

Due to the absence of targetable receptors, the management of TNBC relies heavily on conventional modalities such as surgery, radiotherapy, and cytotoxic chemotherapy.[5] Standard chemotherapy regimens, including anthracyclines and taxanes, remain the mainstay of treatment, both in the adjuvant and metastatic settings. Despite initial chemosensitivity, TNBC patients often experience early relapse and a poorer overall survival rate compared to other breast cancer subtypes. The overall prognosis for patients with metastatic TNBC (mTNBC) remains dismal, with median overall survival rarely exceeding 12-18 months even with

1. MBBS, FCPS, Assistant Professor Radiotherapy, Quaid e Azam Medical College, Bahawalpur, Pakistan.
2. MBBS, FCPS, Assistant Professor Clinical Oncology, Nishtar Medical University, Multan, Pakistan.

Correspondence Address:
Dr. Asima Luqman
Department of Radiotherapy, Quaid e Azam Medical College, Bahawalpur, Pakistan.
asimaluqman@gmail.com

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aggressive treatment.[6]

In recent years, there has been increasing interest in the use of metronomic chemotherapy as an alternative therapeutic strategy for mTNBC. Metronomic chemotherapy is defined as the frequent, regular administration of chemotherapeutic agents at relatively low, minimally toxic doses, with no prolonged drug-free breaks.[7] This approach is fundamentally different from conventional maximum-tolerated dose regimens, as it primarily exerts its antitumor effects through antiangiogenic mechanisms. By targeting the endothelial cells of the tumor vasculature, metronomic chemotherapy inhibits neo-vascularization, leading to sustained apoptosis within the tumor microenvironment and limiting the tumor's ability to grow and metastasize. Preclinical studies have shown that continuous low-dose administration of agents such as capecitabine can suppress tumor angiogenesis, modulate the immune response, and reduce the emergence of drug-resistant clones. Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), has demonstrated promising activity in various settings of breast cancer, including as part of metronomic regimens. When used in a metronomic schedule, capecitabine offers several potential advantages as it is orally administered, which increases convenience and compliance; it provides sustained exposure to the tumor; and it is generally associated with a more favorable toxicity profile compared to high-dose chemotherapy.[8] Clinical trials and retrospective analyses have suggested that metronomic capecitabine may offer a reasonable balance between efficacy and tolerability, maintaining disease stability and prolonging progression-free survival (PFS) while minimizing severe adverse events.[9,10] This is particularly important in the metastatic setting, where maintaining quality of life and reducing hospitalizations are critical goals alongside disease control.

Despite accumulating evidence, metronomic capecitabine remains underutilized, and its precise role in the management of mTNBC continues to evolve.[11] Given the aggressive biology of mTNBC, the lack of effective targeted therapies, and the limitations of current chemotherapeutic strategies, there is a pressing need to explore alternative, patient-friendly regimens that can provide durable clinical benefit without imposing excessive toxicity. The present study was therefore designed to address these critical gaps in knowledge and clinical practice. It aimed to evaluate the efficacy of metronomic capecitabine in prolonging PFS in patients with mTNBC, while also systematically assessing its safety and tolerability profile. By focusing on these endpoints, this research seeks to provide oncologists with evidence-based guidance on a potentially valuable therapeutic option for a patient population with otherwise limited treatment choices. Ultimately, improving outcomes for patients with mTNBC requires innovative, individualized approaches, and metronomic chemotherapy may represent a significant step forward in this direction.

METHODS

This retrospective study was conducted at the department of radiotherapy, Quaid e Azam Medical College, Bahawalpur, Pakistan, during 1st January 2022 to 30th October 2025. Being a retrospective study, exemption was obtained from Institutional Ethical Review Board (letter number: 548/DME/QAMC Bahawalpur, dated: 04-12-2025). Data of all eligible cases during the study period were identified from hospital records and included for analysis. The study included patients with mTNBC of any age who were metastatic at presentation. Baseline laboratory tests, chest X-ray, and abdominal ultrasound were done. CT scans of the chest, abdomen, and pelvis were performed at initiation. As this was a retrospective review of existing records, informed consent was not required in accordance with institutional policy. All patients received first-line chemotherapy, or subsequently went on to receive the second-line chemotherapy. Capecitabine at a dose of 500 mg twice daily was administered to patients with stable disease after initial chemotherapy. Patients were asked to follow up every 4 weeks and thorough clinical examination was performed at each follow up. CT scans of the chest, abdomen, and pelvis were repeated after 4 months detect any new metastatic sites. MRI of the brain was conducted for symptomatic patients. PFS was defined as stable disease for a period of 4 months. Toxicity profile associated with metronomic capecitabine was also noted.

Data was analyzed using IBM-SPSS Statistics, version 26.0. Frequency and percentages were showed for qualitative data. Mean and standard deviation, or median and inter-quartile range (IQR) were calculated for quantitative data. Chi-square test was used to compare categorical data whereas quantitative data were compared employing independent sample t-test of Mann-Whitney U test. P value below 0.05 was taken as significant.

RESULTS

Out of 643 breast cancer patients, 117 (18.2%) had stage IV disease, with 47 (40.1%) having mTNBC. The median age was 44 years (range: 32-76 years). Among mTNBC patients, 26 (55.3%) were pre-menopausal. There were 30 (63.8%) patients who had bone metastases, and 17 (36.1%) had visceral metastases. Table-I is showing details about the demographical and clinical information of mTNBC cases.

All patients received first-line chemotherapy, and 41 (87.2%) went on to receive second-line chemotherapy. There were 33 (70.2%) patients who achieved stable disease and started metronomic capecitabine following initial chemotherapy. Among these 33 patients, 24 (72.7%) had stable disease while remaining 9 (27.3%) experienced disease progression, indicated by an increase in the size or site of metastasis. Table-2 is showing comparison of demograhical and clinical data with respect to disease status following metronomic capecitabine treatment.

TABLE-I

Demographical and clinical information (n=47)

Demographical and clinical information			Number (%)
Age, median (IQR)			44 (32-76)
Residence	Rural		31 (66.0%)
	Urban		16 (34.0%)
Menopausal status	Pre-menopausal		26 (55.3%)
	Post-menopausal		21 (44.7%)
Site of metastasis	Bone		30 (63.8%)
	Visceral	Liver	10 (21.3%)
		Lungs	5 (10.6%)
		Brain	2 (4.3%)

The most common toxicities were mild nausea and vomiting, noted in 9 (27.2%), grade 1 diarrhea 4 (12%), grade 1 mucositis 3 (9.1%), and grade 1 myelosuppression 4 (12.4%). Figure-1 is showing Comparison of distribution frequency of toxicity profile among patients undergoing metronomic capecitabine treatment with respect to disease outcome.

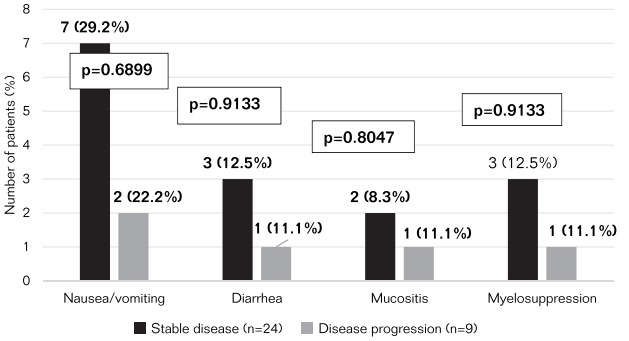
TABLE-II

Comparison of demograhical and clinical data with respect to disease status following metronomic capecitabine treatment (N=33)

Study Variables			Stable Disease (n=24)	Disease Progression (n=9)	P-Value
Age, median (range)			44 (32-76)	42 (32-72)	0.5261
Residence	Rural		18 (75.0%)	5 (55.6%)	0.2790
	Urban		6 (25.0%)	4 (44.4%)	
Menopausal status	Pre-menopausal		14 (58.3%)	4 (44.4%)	0.4755
	Post-menopausal		10 (41.7%)	5 (55.6%)	
Site of metastasis	Bone		16 (66.7%)	5 (55.6%)	0.6709
	Visceral	Liver	5 (20.8%)	2 (22.2%)	
		Lungs	2 (8.3%)	2 (22.2%)	
		Brain	1 (4.2%)	-	
Toxicity profile frequency	Nausea/vomiting		7 (29.2%)	2 (22.2%)	0.6899
	Diarrhea		3 (12.5%)	1 (11.1%)	0.9133
	Mucositis		2 (8.3%)	1 (11.1%)	0.8047
	Myelosuppression		3 (12.5%)	1 (11.1%)	0.9133

FIGURE-1

Comparison of toxicity profile among patients undergoing metronomic capecitabine treatment with respect to disease outcome (N=33)



DISCUSSION

This study's findings revealed that metronomic capecitabine was associated with a high rate of disease stabilization and an acceptable toxicity profile. Our study found that 72.7% of patients with mTNBC maintained stable disease after 4 months of metronomic capecitabine treatment, while 27.3% experienced disease progression. This outcome is noteworthy, as the high proportion of stable disease highlights the potential of metronomic capecitabine as an effective therapeutic option for mTNBC patients. The findings align with Montagna et al.[11], reported a 71% PFS rate at 4 months in a cohort of patients with various subtypes of breast cancer, including TNBC. However, Montagna et al.[11], found a lower overall PFS rate at 1 year (34%) and emphasized a significantly higher PFS in patients with ER-positive tumors compared to those with ER-negative tumors (65% vs. 15%, p=0.046). This suggests that while metronomic capecitabine is effective in the short term, its long-term efficacy need evualuation, particularly in patients with ER-negative tumors, including TNBC. Yoshimoto et al.[12], reported a median PFS of 10.7 months in TNBC patients treated with a combination of capecitabine and cyclophosphamide. The higher median PFS observed in the Yoshimoto study may be attributed to the inclusion of cyclophosphamide, which could have provided additional therapeutic benefit. However, the small sample size of TNBC patients in that study (n=9) limits the generalizability of the findings. The longer follow-up period in Yoshimoto et al study (18.1 months) might have allowed for a more comprehensive assessment of the regimen's efficacy over time.[13] In contrast, our study's shorter evaluation period of 4 months provides a snapshot of the early benefits of metronomic capecitabine, underscoring its potential as a first or second-line therapy in mTNBC. Weadick et al.[14], study offered another point of comparison, particularly in terms of time on treatment and progression. They reported a mean time on treatment of 5.04 months for TNBC patients receiving metronomic therapy, with a range of 0.46-16.69 months. This finding, alongside our study's results, suggested that while metronomic capecitabine can achieve disease stabilization in the short term, its efficacy may diminish over longer periods, necessitating dose adjustments or treatment changes. Weadick et al.[14], also highlighted the higher proportion of disease progression (72.9%) as the primary reason for ending treatment, which contrasts with our study, where a significant majority achieved stable disease. He et al.[15], study, which assessed the efficacy of pyrotinib combined with metronomic capecitabine in HER2-positive metastatic breast cancer, reported a median PFS of 11.9 months and a CBR of 81.6%. Although this study focused on HER2-positive patients, the combination of pyrotinib and metronomic capecitabine demonstrated significant clinical benefit, particularly in terms of PFS.

In contrast, our study, which focused solely on mTNBC patients, reported a shorter-term PFS at 4 months, underscoring the challenges of treating this more aggressive subtype. VICTOR-2 tria reported a relatively higher median PFS of 4.7 months[16], which could be attributed to the use of a combination therapy rather than capecitabine alone. VICTOR-2 trial highlighted a clinical benefit rate of 53.7%, suggesting that metronomic chemotherapy can offer disease control even those with TNBC. However, the slightly higher median PFS in the VICTOR-2 trial compared to our study may reflect the benefits of combination therapy, which could be explored further in future research to enhance the efficacy of metronomic capecitabine in mTNBC.[16]

This study also demonstrated that metronomic capecitabine was associated with a manageable toxicity profile, with the most common adverse events being mild nausea and vomiting (27.2%), grade 1 diarrhea (12%), grade 1 mucositis (9.1%),

and grade 1 myelosuppression (12.4%). Importantly, no cases of severe toxicity, such as hand-foot syndrome or neuropathy, were reported, which aligns with the findings from Alagizy et al. In their phase II study, metronomic capecitabine was well tolerated, with 31.7% of patients developing grade 1 hand-foot syndrome, 12.2% experiencing grade 1 diarrhea, and 4.9% having grade 1 vomiting.[17] The absence of severe hematological, hepatic, or renal toxicities by others mirror the present findings, reinforcing the safety of metronomic capecitabine in this patient population.[15] Weadick et al.[14], reported a higher incidence of dose reductions (37.8%) due to toxicities such as decreasing performance status, palmoplantar syndrome, and cytopenia, with a more pronounced impact observed in the Swedish cohort. The indications for dose reduction including palmoplantar syndrome (26%) and cytopenia (21%), suggest that while metronomic capecitabine is generally well tolerated, specific patient factors may necessitate treatment modifications.[14] Montagna et al.[12], found nausea, and diarrhea as the most frequent treatment related side effects. This aligns with our findings, where the toxicities were mostly mild and manageable. The absence of severe adverse events in our study suggests that metronomic capecitabine can be administered with relative safety, even in a population with metastatic disease.[18-21]

The clinical implications of this research are significant, particularly for the management of mTNBC, a subtype of breast cancer that is notoriously difficult to treat due to its lack of targeted therapies. The present study presents metronomic capecitabine as a valuable approach in maintaining disease control in mTNBC patients.[22,23] Reliativley lower and less severe toxicity spectrum may further allow sustainable treatment approach without increasing the severity of treatment related side effects, that can contribute to improvement in quality of life of these patients.[24,25] Given the high rates of stable disease at 4-month perior, exploring long-term effectiveness of metronomic capecitabine in mTNBC will add valuable insights. Identifying biomarkers that predict response to metronomic capecitabine could help tailor treatment to individual patients, potentially enhancing its efficacy.

Retrospective nature of this research prevented us in real time prospective analysis of study participants. Small sample size and a relatively short-term outcome evaluation were some of the other inherent limitations of this study. Further multicenteric studies involving long-term evaluation can further add about the role of metronomic capecitabine in mTNBC.

CONCLUSION

Metronomic capecitabine was to be an effective and well-tolerated approach in patients having mTNBC, escpecially in the short-term. High rates of stable disease and manageble spectrum of toxicity profile underscores the potential of metronomic capecitabine as a precious therapeutic approach in mTNBC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Asima Luqman:** Data collection, analysis, writing.
2	**Sarah Khan:** Conception, design, proof reading, critical revisions.