INTRODUCTION

Triple-negative breast cancer (TNBC) is a heterogeneous subtype of breast cancer marked by lack of expression of the estrogen receptor, progesterone receptor, and HER2 (human epidermal growth factor receptor 2). It accounts for 12% to 17% of all breast cancers. TNBC has significant variability in morphological and pathological features and a tendency to relapse with distant metastases earlier than other forms of breast cancer. TNBC has some characteristic clinico-pathologic features like young age at the time of presentation, large size of the tumor, and higher incidence of node positivity at presentation. TNBC documents a higher recurrence within 2 years of diagnosis and decreased 5-year survival rate. Women with TNBC do not benefit from endocrine therapy or trastuzumab. Management of the disease at present involves the use of a third-generation chemotherapeutic regimen similar to that offered to other high-risk patients, due to lack of any definitive guidelines. However, despite the chemosensitivity and the promising initial response, there is a high risk of relapse and poor overall survival in the majority of patients with residual disease.

Metronomic chemotherapy refers to chemotherapy regimen in which frequent administration of drugs at doses below the maximum tolerated dose (MTD) without a prolonged drug-free break is achieved. It attains sustained low blood levels of the drug without any significant toxic sideeffects, and hence reduce the need for supportive therapy in these patients. It exerts direct and indirect effects on the tumor by targeting the tumor cells along with their microenvironment. The mechanism of action of metronomic chemotherapy is by inhibition of tumor angiogenesis. Unlike conventional chemotherapy which targets proliferating tumor cells, it targets the endothelial cells in the growing tumor vasculature. It also acts via stimulation of the immune response by inducing a selective reduction in circulating regulatory T cells.

A metronomic therapy schedule of methotrexate and cyclophosphamide was evaluated by Mross et al., which showed an overall clinical benefit of 31.7% (95% CI, 20.6–44.6%), tolerable toxicity [grade 1...
and 2 neutropenia (20.6%), anemia (9.5%) and elevated liver enzymes (0.9%). The current article is aimed at reporting 22 cases of TNBC who underwent maintenance metronomic therapy (methotrexate and cyclophosphamide) after routine chemotherapy and radiotherapy.

**CASE SERIES REPORT**

All 22 patients reported in this case series were clinically and histopathologically diagnosed with TNBC at curable stages (Stage I to Stage IV). They had minimal metastasis without visceral crisis. Both pre-and post-menopausal patients were included after obtaining written informed consent. The average age of patients included in this report was 47 years. The left breasts (54.5%) were found to be slightly more predisposed than the right (45.5%). Out of 22 patients, 12 were post-menopausal. The pathological TNM staging grouped 1 patient each in stage I and IV, 2 patients in stage IIc, and 5, 6, and 7 patients respectively in Stage IIa, IIa, and IIb.

**Treatment regimen**

- Chemotherapy and radiotherapy were administered to all the patients as per NCCN (National Comprehensive Cancer Network) guidelines [Figure 1].
- Chemotherapy schedules included Fluorouracil, Adriamycin, and Cytoxan (FAC), Paclitaxel + carboplatin.
- After completing the treatment schedule patients were given T.Cyclophosphamide 50mg OD x 14 days with T.Methotrexate 10 mg/week x 2weeks followed by one week off. A total of a 3-week cycle for one-year duration was administered.

All patients underwent surgical intervention with either MRM (modified radical mastectomy) or BCS (breast-conserving surgery). Among these, adjuvant chemotherapy with 4 cycles of FAC was given to 8 patients, along with 4 cycles of PMRT (post-mastectomy radiation therapy) in 2 patients and without PMRT in 1 patient, with 4 cycles of Paclitaxel without RT in 1 patient, 4 cycles of TC (Taxotere and Cyclophosphamide) with PMRT in 1 patient and without RT in 3 patients. Two patients received 6 cycles of FAC with PMRT, and 4 cycles and 6 cycles of NACT (neoadjuvant chemotherapy) FAC followed by 4 cycles of Paclitaxel and carboplatin post-surgery and PMRT was done in two patients respectively. In one patient 4 cycles of NACT FAC was accompanied by 4 AC and post-operatively 4 TC with PMRT and without PMRT in 1 patient. One patient received 4 cycles of AC and 4 cycles of TC along with PMRT after BCS. (Table 1)

**Follow up**

- After completion of the treatment protocol, follow-up was done according to the NCCN guidelines.
- Regular clinic visits were scheduled every month for 18 months followed by 3 monthly visits for 2 years, and annually thereafter.
- In each visit, patients were evaluated by case history, physical examination, and X-ray mammography.
- After one year patients were re-evaluated with whole-body PET CT to rule out metastasis.

One patient expired (due to secondaries in the brain), one patient progressed with secondaries in the lung, and 3 were lost after a follow-up of 25, 27, and 40 months respectively. The mean overall survival (OS) was 28.65 months in 20 patients and the overall distant metastasis recurrence rate during the follow-up period was 9% (2 of 22). The median OS was 29 months.

Adverse reactions to therapy were evaluated, and Grade 1 neutropenia was seen in 4 patients (resolved with observation and delay in starting next cycle). Grade 1 Vomiting was seen in 5 patients, and Grade 1 diarrhoea was present in 2 patients. One patient exhibited grade 1 oral mucositis which was managed with conservative treatment.

**REVIEW OF LITERATURE**

Approximately one-quarter of the breast cancers belong to the molecular subtype of TNBC. Dent R et al reported that patients in the TNBC cohort are relatively younger. The majority of the patients have grade III tumors with the tumor size being larger (>2 cm) compared to the other subtypes. The rate of node positivity is also reported to be higher in TNBC, independent of the size of the tumor.[1] Early mortality with TNBC is afact with a median time to death of 4.2 years when compared to 6 years for other cancer types (p<0.0001). Also, TNBC patients have a higher risk of mortality when compared to other cancer types (42.2% versus 28%, respectively; P < 0.0001).

In comparison to other breast cancer types, TNBC doesn’t fair in recurrence rates as well. A higher proportion of TNBC shows distant recurrence with a lower mean time to recurrence (2.6 years), while the same is higher for other cancer types (5 years). As opined in a study by Cazzaniga et al., the median time to relapse post radical surgery is approximately 18 months for TNBC.[1] This re-establishes the median overall survival at <24 months.[2] These clinical features and recurrence patterns have fated TNBC to be one of the cancers with poor prognosis even at its early stages. TNBClacks expression of the progesterone receptor, estrogen receptor, and HER2.[2] Management is a challenge in such cases where endocrine therapy or targeted therapies to HER2 is ineffective and results in a poor outcome. This scenario warrants a special treatment approach. In the last few years, metronomic chemotherapy has shown promising results in improving the prognosis and this case series proves the same for the South Indian population. Metronomic therapy is the
application of conventional chemotherapy in low
doses with minimal toxicity, at regular intervals
with no large breaks in treatment. They act by
triggering the immune system while inhibiting
angiogenesis and have proven to be clinically
beneficial.12

Various animal studies, pre-clinical and clinical
studies viz. Topotecan (a topoisomerase I inhibitor)
in animal, in-vitro and human studies; metronomic
topotecan with pazopanib in mice, metronomic oral
vinorelbine in two phase II trials, and one-year
capcitabine metronomic chemotherapy phase II
trials showed advanced anti-tumor activity with an
effective decrease in tumor vascularity along with
good tolerability and safety.12 A pilot study on
Metronomic Docetaxel showed very promising
results on the survival benefits as well. However,
all these drugs needed further evaluation of their
efficacy and safety in phase III randomized clinical
trials.

We analyzed metronomic cyclophosphamide and
methotrexate combination post standard therapy and
revealed a mean OS of 28.65 months in 20 patients
suffering from TNBC. The median OS in our
findings was 29 months. In a phase III study, Nasr
KE et al investigated the role of maintenance
metronomic therapy with a similar regimen of oral
methotrexate plus Cyclophosphamide given for 1
year after finishing the adjuvant treatment for
patients with TNBC in prolonging their disease-free
interval.13 The median OS for the patients on
maintenance metronomic therapy was 37 months
while the median disease-free survival (DFS) for
the same group was 28 months. They recorded a 26%
overall distant metastasis recurrence rate during the
follow-up period, while our study recorded only 9%
(2 out of 22 patients). This could be attributed to
the longer follow-up period and study duration
compared to our study. They also recorded a
significant difference in DFS, OS, and the overall
distant metastasis recurrence rates in comparison
to patients who were not given the maintenance
metronomic therapy (p-value <0.05).12,13

The most common side effect reported in the phase
III study was neutropenia followed by febrile
neutropenia.14 The treatment protocol was reported
to be well tolerated. Another study (Kontaniet al.)
also reported significant improvement of OS and a
mild toxicity profile with metronomic therapy in
metastatic breast cancer.14 Our study reflected a
similar safety profile with 4 out of 22 patients
demonstrating grade 1 neutropenia. Yet another
phase II study (Torrisi et al.) tested adjuvant
metronomic chemotherapy by cyclophosphamide
and methotrexate for 6 months post 3 cycles of ECF
(epirubicin, cisplatin, and fluorouracil as continuous
infusion) followed by 3 cycles of weekly paclitaxel
in 30 women and reported a 20% incidence of grade
>2 non-hematological toxicities.15 These adverse
effects are very severe when compared to safety
findings from our study. Leukopenia, decreased
haemoglobin, and hand foot syndrome were other
adverse events reported in studies conducted on the
use of metronomic cyclophosphamide in
combination with paclitaxel and capecitabine.16,17
The incidence of severe adverse events might be
associated with the combined use of capecitabine in
these studies. However, the smaller sample tested
avoids extrapolation of the safety and tolerability
data to the TN cohort.

The IBCSG (International Breast Cancer Study
Group) Trial 22-00 analysis at the end of 7-year
follow-up reported that disease-free survival does
not significantly improve with the addition of
maintenance metronomic therapy.18 Nevertheless,
the sub-analysis on TN patients assigned to
cyclophosphamide – methotrexate combination
maintenance arm showed a relative reduction of
DFS events (24%) despite the high nonadherence
observed in this group. Though the results derived
were not statistically significant, it warrants further
investigation because of the dearth of guidelines and
targeted therapies for TNBC.

![Figure 1: Treatment regimen followed in all cases. MRM- modified radical mastectomy; PMRT- post mastectomy radiation therapy, LABC- locally advanced breast cancer](image)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Age (years)</th>
<th>Stage</th>
<th>Treatment regimen</th>
<th>chemotherapy completion</th>
<th>Overall survival till 7/20 (months)</th>
<th>Survival status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>67</td>
<td>pT3 N0M0 stage IIB Lymphovascular invasion</td>
<td>Right MRM + AC 4FAC+ 4 TC+ PMRT</td>
<td>6/2019</td>
<td>30</td>
<td>On Follow up(FU)</td>
</tr>
</tbody>
</table>

Table 1: Summary of clinicopathological characteristics, treatment and outcome of TNBC with maintenance metronomic therapy in 22 cases

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144
2. **pT2N0M0**  
   Stage IIA  
   LVI negative  
   Right MRM + AC  
   4FAC + 4 Paclitaxel + carboplatin  
   No RT  
   5/2019  
   32  
   FU

3. **pT2N1 M0**  
   stage IIB  
   LVI positive  
   Right MRM + AC  
   4FAC + 4TC + PMRT  
   5/2020  
   21  
   FU

4. **pT2N0 M0**  
   Stage IIA  
   LVI positive  
   Right MRM + AC  
   4FAC + 4TC + PMRT  
   9/2019  
   25  
   Lost FU in March 2020

5. **pT2N1M0**  
   Stage IIB  
   LVI positive  
   Left MRM + AC  
   4FAC + 4TC + PMRT  
   Jan 2018  
   Developed DCM with CCF in 9/2019  
   27  
   Lost FU in December 2019

6. **pT2N0M0**  
   Stage IIA  
   LVI negative  
   Left MRM + 6FAC + 4TC + PMRT  
   7/2019  
   40  
   Lost FU in May 2020

7. **cT4d N1 M0**  
   stage IIB  
   LVI positive  
   Left MRM + 4 cycles NACT FAC  
   Left MRM+ 4 Paclitaxel, carboplatin + PMRT  
   3/2020  
   24  
   FU

8. **cT4d N3 M1**  
   C/L ScI and axillary Ln stage IV  
   LVI positive  
   6 FAC + MRM+ 4 Paclitaxel + carboplatin + PMRT  
   6/2020  
   20  
   FU

9. **pT2N2M0**  
   Stage IIIA  
   LVI positive  
   Right MRM + 4 FAC + 4TC  
   4/2020  
   22  
   FU

10. **pT3N0M0**  
    Stage IIB  
    LVI positive  
    Left MRM + 4 FAC + 4 TC  
    1/2020  
    29  
    FU

11. **cT4d N3 M0**  
    stage IIIC  
    LVI positive  
    4FAC + left MRM + 4 TC  
    12/2019  
    30  
    FU

12. **pT2N1 M0**  
    Stage IIB  
    LVI positive  
    MRM + 4 FAC + 4TC + PMRT  
    Secondary progression in lungs  
    OS till now  
    FU

13. **pT1N0M0**  
    stage I  
    LVI positive  
    Right BCS + 4AC + 4TC + PMRT  
    8/2019  
    29  
    FU

14. **cT4b N3 M0**  
    stage IIIC  
    LVI positive  
    NACT  
    4FAC + MRM + 4TC + PMRT  
    7/2020  
    18  
    FU

15. **cT4b N1 M0**  
    stage IIIA  
    LVI positive  
    NACT + Left MRM  
    4AC + 4TC  
    Patient expired due to secondary progression in brain  
    -  
    -

16. **pT2N0M0**  
    stage IIIA  
    LVI positive  
    Right MRM  
    4FAC + 4TC + PMRT  
    1/2020  
    25  
    FU

17. **pT3N1M0**  
    stage IIIA  
    LVI positive  
    Left MRM  
    4FAC + 4TC + PMRT  
    3/2019  
    37  
    FU

18. **cT3N1M0**  
    Stage IIIA  
    LVI positive  
    4FAC + Left MRM + 4TC  
    3/2020  
    24  
    FU

19. **pT2N1M0**  
    stage IIIA  
    LVI positive  
    Left MRM + 4FAC + 4TC + PMRT  
    1/2019  
    36  
    FU

20. **pT3N1M0**  
    stage IIIA  
    LVI positive  
    Left MRM + 4AC + 4TC + PMRT  
    6/2018  
    41  
    FU

21. **pT2N0M0**  
    stage IIIA  
    LVI positive  
    Left MRM + 4AC + 4TC + PMRT  
    1/2019  
    34  
    FU

22. **pT3N0M0**  
    stage IIIA  
    LVI positive  
    Right MRM + 4AC + 4TC + PMRT  
    6/2019  
    29  
    FU

MRM - Modified Radical Mastectomy; BCS - Breast Conserving Surgery; AC - Adjuvant chemotherapy; FAC - Fluorouracil, Adriamycin and Cytoscan; PMRT - Post Mastectomy Radiation Therapy; TC - Taxotere and Cyclophosphamide.
CONCLUSION

Metronomic chemotherapy provides a minimum biologically effective dose of a chemotherapeutic agent in a continuous dosing regimen, without prolonged drug-free periods leading to superior antitumor activity in TNBC. However, the lack of adequate data and defined protocols regarding the use of metronomic therapy in TNBC patients have been a deterrent for its widespread clinical application. The right selection of patients and the right choice of drugs, both with regard to doses as well as schedules, are crucial factors for determining the success or the failure of metronomic chemotherapy in the adjuvant setting. Considering that there is no universally accepted standard chemotherapy regimen for adjuvant treatment of TNBC different authors tested alternative strategies intending to improve relapse-free survival. The analysis of our cases demonstrated a significant improvement in the survival and good tolerability with a maintenance metronomic therapy of methotrexate and cyclophosphamide, after routine chemotherapy and radiotherapy. However, further trials with longer follow-up and a bigger sample size are needed to substantiate the claims further to improve the prognosis for this aggressive disease.

REFERENCES