Section: Medicine

Original Research

TREATMENT OUTCOME AND PROGNOSIS OF TNBC WITH MAINTENANCE METRONOMIC THERAPY- A REPORT OF 22 CASES WITH REVIEW OF LITERATURE

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Abstract

Background: Triple-negative breast cancer (TNBC) is a heterogeneous subtype of breast cancer. Currently, there is no universally accepted standard chemotherapy regimen for adjuvant treatment of TNBC. The analysis of our cases has demonstrated a significant improvement in the survival and good tolerability with a maintenance metronomic therapy. **Materials and Methods:** All 22 patients were diagnosed with TNBC at curable stages (Stage I to Stage IV) and had minimal metastasis without visceral crisis. 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. **Result:** 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. One patient had MRM (modified radical mastectomy) followed by BCS (breast-conserving surgery) treatment. **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. The lack of adequate data and defined protocols regarding the use of metronomic therapy has been a deterrent for its widespread clinical application.

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.[1] TNBC has significant variability in morphological and pathological features and a tendency to relapse with distant metastases earlier than other forms of breast cancer.[2] TNBC has some characteristic clinicopathologic 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.1 Women with TNBC do not benefit from endocrine therapy or trastuzumab.[3] 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.[4] 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 toa 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 reducesthe need forsupportive therapy in these patients.[5] It exerts direct and indirect effects on the tumor by targeting the tumor cells alongwith 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.[6] It also acts via stimulation of the immune response by inducing a selective reduction in circulating regulatory T cells.[7]

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

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and 2 neutropenia (20.6%)], anemia (9.5%) and elevated liver enzymes (0.9%)].[8] 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 histopathologic ally 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 IIIc, and 5, 6, and 7 patients respectively in Stage IIa, IIIa, 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, andX-ray mammography.
- After oneyear 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.[2] 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.[9] This re-establishes the median overall survival at <24 months.[10] 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.[11] 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 seriesproves the same for the South Indian population. Metronomic therapy is the

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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, andone-year capecitabine metronomic chemotherapyin 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.13However, 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.[1] The median OS for the patients on maintenance metronomic therapy was 37 months while the mediandisease-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).[13,14]

The most common side effect reported in the phase III study wasneutropenia followed by febrile neutropenia.[1] 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.14Our 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] Theincidence 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 22-00analysis 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.

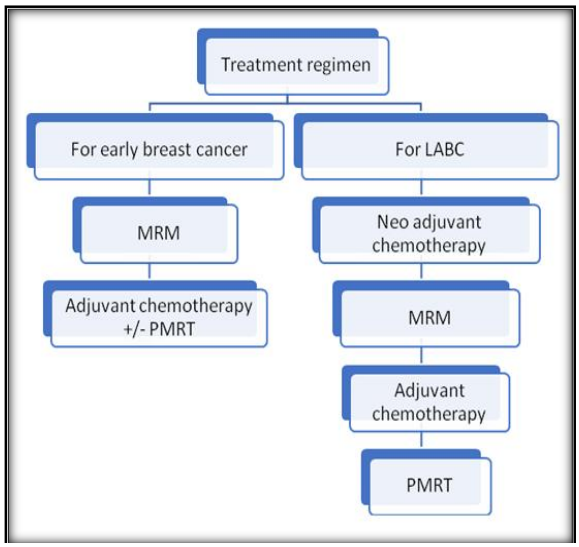

Figure 1: Treatment regimen followed in all cases. MRM- modified radical mastectomy; PMRT- post mastectomy radiation therapy, LABC- locally advanced breast cancer

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

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

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		(LVI)positive				
2.	57	pT2N0M0 stage IIA LVI negative	Right MRM+ AC 4FAC + 4 Paclitaxel+ carboplatin No RT	5/2019	32	FU
3.	51	pT2N1 M0 stage IIB LVI positive	Right MRM+ AC 4FAC+4TC+PMRT	5/2020	21	FU
4.	55	pT2N0 M0) Stage IIA LVI positive	Right MRM+ AC 4 FAC+ 4TC+PMRT	9/2019	25	Lost FU in March 2020
5.	50	pT2N1M0 Stage IIB LVI positive	Right MRM 6FAC +4TC+PMRT.	Jan 2018 Developed DCM with CCF in 9/2019	27	Lost FU in December 2019
6.	61	pT2N0M0 stageIIA LVI negative	Left MRM+ 6FAC+4TC+PMRT	7/2019	40	Lost FU in May 2020
7.	49	cT4d N1 M0 stageIIIA LVI positive	4 cycles NACT FAC Left MRM+ 4 Paclitaxel, carboplatin + PMRT	3/2020	24	FU
8.	47	cT4d N3 M1 C/L Scl and axillary Ln stageIV LVI positive	6 FAC +MRM+ 4 Paclitaxel + carboplatin + PMRT	6/2020	20	FU
9.	55	pT2N2M0 stage IIIA LVI positive	Right MRM + 4 FAC+4TC	4/2020	22	FU
10.	38	pT3N0M0 stage IIB LVI positive	Left MRM+ 4FAC+ 4 TC	1/2020	29	FU
11.	40	CT4d N3 M0 stageIIIC LVI	4FAC + left MRM + 4 TC	12/2019	30	FU
12.	43	pT2 N1 M0 stage IIB LVI positive	MRM + 4 FAC + 4TC +PMRT	Secondary progression in lungs	OS till now	FU
13.	22	pT1N0M0 stage I LVI positive	Right BCS + 4AC +4TC+ PMRT	8/2019	29	FU
14.	51	cT4b N3 M0 stage IIIC LVI positive	NACT 4FAC + MRM + 4TC + PMRT	7/2020	18	FU
15.	36	cT4b N1 M0 stage IIIA LVI positive	NACT + Left MRM 4AC + 4TC	Patient expired due to secondary progression in brain	-	-
16.	51	pT2N0M0 stage IIA LVI positive	Right MRM 4FAC+4TC+PMRT	1/2020	25	FU
17.	50	pT3N1M0 stage IIIA LVI positive	Left MRM 4FAC+4TC+PMRT	3/2019	37	FU
18.	35	cT3N1M0 Stage IIIA LVI positive	4FAC + Left MRM + 4TC	3/2020	24	FU
19.	50	pT2N1M0 stage IIB LVI positive	Left MRM + 4FAC+4TC+PMRT	1/2019	36	FU
20.	48	pT3N1M0 stage IIIA LVI positive	Left MRM + 4AC+4TC+PMRT	6/2018	41	FU
21.	21	pT2N0M0 stage IIA LVI positive	Left MRM + 4AC+4TC+PMRT	1/2019	34	FU
22.	55	pT3N0M0 stage IIB 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 Cytoxan; PMRT- Post Mastectomy Radiation Therapy; TC-Taxotere and Cyclophosphamide.

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CONCLUSION

Metronomic chemotherapy providesa 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 improverelapse-free survival. The analysis of our caseshas demonstrated a significant improvement in the survival and goodtolerability 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.

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