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ORIGINAL ARTICLE

Efficacy of low-dose metronomic chemotherapy with 2 drugs versus 3 drugs oral regimen in metastatic breast cancer patients.

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ABSTRACT… Objective: To investigate the effectiveness of two drugs (cyclophosphamide and methotrexate) compared to three drugs (cyclophosphamide, methotrexate, and capecitabine) in treating MBC. **Study Design:** Retrospective study. **Period:** September 21, 2021, and December 31, 2022. **Setting:** Oncology Unit, Nishtar Hospital Multan. **Methods:** This study involved 80 female patients with metastatic breast cancer (MBC) who were selected consecutively. The participants were divided into groups A and B, consisting of 40 patients. Group A received two oral LDMC medications, cyclophosphamide and methotrexate. In comparison, group B received three medications: cyclophosphamide, methotrexate, and capecitabine. **Results:** In the study, it was observed that 27.5% of participants in group A exhibited disease control rate, whereas 60% of patients in group B showed disease control rate (p=0.014). The mean progression free survival was 10.5 weeks in group A and 19.7 weeks in group B (p=0.039). The mean duration of response was 27.4 weeks in group A and 35.5 weeks in group B (p=0.412). **Conclusion:** This retrospective research has demonstrated that using the low-dose metronomic chemotherapy (LDMC) treatment with a three-medicine combination regimen significantly improved outcomes in patients with metastatic breast cancer (MBC). The observed disease control rate (DCR) was considerably higher.

Key words: Cyclophosphamide, Chemotherapy, Capecitabine, Metastatic Breast Cancer, Methotrexate.

INTRODUCTION

Metastatic breast cancer (MBC) is a frequent condition in women with high mortality and morbidity as it is incurable. However, the disease can be treated and it is important to improve illness management while maintaining quality of life (QoL).[1] In recent times, low-dose metronomic chemotherapy (LDMC) has acquired growing success in the previous decades.[2,3] The chemotherapy involves administering low doses of cytotoxic medicines, significantly less than the dosage administered in conventionally.[4] Lower dosages of chemotherapeutic medications may result in fewer side effects such as bone marrow suppression, mucositis, or baldness.[5,6,7] Literature has reported that LDMC is more than just a novel method of cancer treatment but a whole new therapeutic approach.[3,8,9] Studies have reported the use of this technique mainly in older individuals that were ineligible to receive conventional therapy.[8]

Drugs such as cyclophosphamide, methotrexate, and capecitabine are used in LDMC as they are administered orally and are well-established in their efficacy. Abundantly successful studies have been done on treatment with LDMC with phase II research, whereas phase III studies are limited. Additionally, to the greatest extent of our understanding, there is inadequate data on the effectiveness of metronomic chemotherapy with two vs three medicines in MBC.

We conducted this study to investigate the efficacy of two LDMC medications (cyclophosphamide and methotrexate) against three medications (cyclophosphamide, methotrexate, and capecitabine) in treating MBC.

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METHODS

This retrospective study was done at the oncology section of Nishtar Hospital Multan between September 21, 2021, and December 31, 2022 after approval from ethical committee (7066-30-06-2024). A total of 80 female patients having metastatic breast cancer (MBC) were included in the study. Patients who had other cancers and those who had received additional treatment like radiotherapy or hormonal therapy, etc. were excluded.

To establish a rigorous study, patients were separated into two groups: Group A and Group B.

The participants were separated into groups A and B, each with 40 patients. Group A was given two oral LDMC medications: cyclophosphamide (50 mg daily) and methotrexate (2.5 mg every other day). In comparison, group B got three medications: cyclophosphamide (50 mg daily), methotrexate (2.5 mg every other day), and capecitabine (600mg/m^2 BID d1–d21).

Since it is provided for palliative treatment for MBC rather than cure, it is given for an indefinite amount of time till the disease is controlled. In those patients who could not endure the adverse effects of chemotherapy, treatment was paused for a while and then resumed once the toxicity was addressed. Disease control rate after 6 months follow up was primary outcome. DCR between subgroups, rate of survival and duration of response were secondary outcomes. Subgroup analysis was also performed regarding the disease control rate in both groups.

Patient records were analyzed to get complete details on patient characteristics, hormone status, metastatic status, toxicological status, and other treatment-related facts. Adverse events were reported to determine each regimen's safety profile.

This study followed ethical norms and received permission from the review board of the institution. All subjects provided informed consent, and patient anonymity was rigorously preserved throughout the study. Statistical analyses were conducted using relevant tests, such as chi-square tests for categorical variables and t-tests for all continuous variables. A p-value < 0.05 was deemed statistically significant.

RESULTS

The research enrolled 80 participants (40 in each group). The patient's details are reported in Table-I. The average age at first diagnoses (FD) for MBC was 59 (34-82) years in group A and 60 (31-82) years in group B ($p = 0.254$). The mean age at the start of therapy was 63.5 (36-82) years in group A and 64.1 (33-84) years in group B ($p = 0.547$). Twenty-three individuals had multiple metastasis sites in group A, and 24 had numerous metastasis sites in group B. Other details of the patient's characteristics can be seen in Table-I. Both groups did not differ significantly in the number or location of metastatic sites (Table-II).

The study found that 27.5% of those who participated in group A had DCR, compared to 60% of group B ($p=0.014$). The mean PFS in group A was 10.5 weeks, but in group B, it was 19.7 weeks ($p = 0.039$). The mean DoR in group A was 27.4 weeks, while in group B, it was 35.5 weeks ($p=0.412$). DCR subgroup analysis shows that 8 out of 16 younger patients in group A achieved DCR, whereas, in group B's younger population, 16 out of 17 patients achieved DCR. The elderly population of both groups showed relatively lower DCR rates than the younger population. HR-positive group A population showed DCR in 25%, while the HR-positive population in group B Showed DCR in 69.2%. Other details of subgroup analysis are shown in Table-IV.

Table-V shows the adverse effects reported in both investigation groups. Both groups experienced similar but manageable side effects, with Group B experiencing a slightly higher number of occurrences than Group A. Neutropenia was encountered in 57.5% of Group B compared to 37.5% in Group A. Occurrence of hand-foot syndrome was reported in just 17.5% in group A, while it was considerably high in group B with 52.5%. During the follow-up period, neither group experienced any symptomatic cardiac events.

The incidence of Mucositus was similar in both groups. Other side effects information among both groups is summarized in Table-V.

Variable	Group A	Group B	P-Value
The mean age at the beginning of treatment (range) (years).	63.5 ± 5.23	64.1 ± 6.34	0.547
The mean age at first diagnosis of MBC (range) (years)	59 ± 5.56	60 ± 6.87	0.254
The mean age at first diagnosis of BC (range) (years)	52 ± 5.43	52 ± 6.22	0.814
The age at which therapy starts			0.578
Younger	16(40)	17(42.5)	
Elderly	24(60)	23(57.5)	
Metastatic sites			1.147
No multiple metastases.	17(42.5)	16(40)	
Multiple metastases.	23(57.5)	24(60)	
HR status			0.475
HR-positive	28(70)	26(65)	
Triple-negative	12(30)	14(35)	

Table-I. Patient demographic details

Variable	Group A	Group B	P-Value
	No. of Patients (%)		
Bone	23 (57.5%)	24 (60%)	0.427
Liver	22 (55%)	23 (57.5%)	1.214
Lung	15 (37.5%)	16 (40%)	0.451
Pleura	7 (17.5%)	9 (22.5%)	0.547
Peritoneum	3 (7.5%)	4 (10.0%)	0.244
Lymph	16 (40%)	15 (37.5%)	0.659

Table-II. Sites of metastasis

Variable	Group A	Group B	P-Value
DCR (n (%))	11(27.5)	24(60)	0.014
Mean PFS (range) (weeks	10.5	19.7	0.039
The mean duration of response (range) (weeks)	27.4	35.5	

Table-III. Response of therapy.

Subgroups	Number of Patients With DCR	DCR% (95% CI)
Whole Group A	11	27.5 (0.14-0.43)
Whole Group B	24	60 (0.16-0.47)
Age		
Younger Group A	8/16	50 (0.17-0.68)
Younger Group B	16/17	94 (0.15-0.49)
Elderly Group A	3/24	12.5 (0.12-0.51)
Elderly Group B	8/23	34.7 (0.18-0.54)
Metastatic sites		
No multi-metastasis Group A	8/17	47 (0.9-0.42)
No multi-metastasis Group B	13/16	81 (0.13-0.52)
multi metastasis Group A	3/23	13 (0.10-0.44)
multi metastasis Group B	11/24	45.8 (0.16-0.47)
HR Status		
HR-positive Group A	7/28	25 (0.7-0.55)
HR-positive Group B	18/26	69.2 (0.6-0.57)
Triple-negative Group A	4/12	33.33 (0.19-0.62)
Triple-negative Group A	6/14	42.8 (0.10-0.60)

Table-IV. Disease control rate in subgroups

Variable	Group A	Group B
Neutropenia	15(37.5)	23 (57.5)
Anemia	17 (42.5)	20 (50.0)
Hand foot syndrome	7 (17.5)	21 (52.5)
Grade 1	5 (12.5)	14 (35.0)
Grade 2	2 (5)	5 (12.5)
Grade 3	0	2 (5)
Sensory neuropathy	11(27.5)	18(45.0)
Heart failure	0	0
Mucositus	19 (47.5)	16 (40)
Gastrointestinal	24 (60)	29 (72.5)
Elevated transaminase	24(60)	27 (67.5)
Asthenia	14 (35.0)	20 (50)

Table-V. Side effects among both Groups.

DISCUSSION

In this retrospective study, 80 MBC patients were examined for the effectiveness of chemotherapy treatment. This study was done at Nishtar Hospital Multan's oncology section and included 80 female patients diagnosed with metastatic breast cancer between September 21, 2021, and December 31, 2022. The participants were

separated into Group A (cyclophosphamide and methotrexate) and Group B (Cyclophosphamide, methotrexate and capecitabine.

The primary endpoint DCR differed considerably between the two groups (27.5% vs. 60%, $p = 0.014$). The results of concomitant metronomic cyclophosphamide and methotrexate therapy in HR-positive and HER2-negative patients, after 6-months follow-up post-treatment, is similar to previous research.[10,11,12] According to current MBC treatment recommendations, elderly and terminal patients who cannot tolerate traditional chemotherapy dosing are often treated by LDMC.[13,14,15] However, we have demonstrated that LDMC can be a therapy choice for younger individuals.

In our research, group B showed a mean PFS range of 19.7 weeks vs 10.5 weeks in Group A. Group B with 3 LDMC showed better results in duration of response than Group A with 2 LDMC (35.5vs217.4) weeks. When Group B with Capecitabine is compared to comparable anticancer efficacy in literature, in our study, the average progression free survival of 19.7 weeks was observed as compared to the 4.2 months as reported by a study on patients with history of MBC.[16]

Both groups showed similar toxicity profiles. Hand foot syndrome was more common in Group B than in Group A (52.5% VS 17.5%); this toxicity rate in Group B was in line with the Study by Samer et al. I.[17] Elevated transaminase levels in up to 60% of patients in both trial groups were primarily due to concurrent hepatic metastases or recovered with a decrease or short suspension of MTX.[11,18,19] Our study found no grade 3 or 4 hepatic toxicity, which is in line with the results obtained by Krajnak et al. I.[18]

Above importantly, our data shows that adding capecitabine to MBC LDMC can dramatically enhance breast cancer patients' survival rates. Researchers are looking ahead to future clinical trials to determine the best capecitabine dosage for breast cancer.

CONCLUSION

This retrospective research has demonstrated that using the low-dose metronomic chemotherapy (LDMC) treatment with a three-medicine combination regimen significantly improved outcomes in patients with metastatic breast cancer (MBC). The observed disease control rate (DCR) was considerably higher.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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