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Efficacy of Intrathecal Therapy In Breast Cancer Patients With Leptomeningeal Metastasis

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ABSTRACT

Leptomeningeal metastases (LM) occurs in approximately 5% of individuals diagnosed with metastatic breast cancer (BC). Both systemic and intrathecal (IT) agents can be used for treatment. However, data to support the effectiveness of IT therapy are insufficient. The primary aim of this study was to assess the efficacy and safety of IT therapy in BC patients with LM.

This was a retrospective observational study. SPSS version 27 was used for statistical analysis. Kaplan–Meier and Cox regression analyses were used for survival analysis.

The study included 14 patients (median age, 52 years). The predominant histopathological types were invasive ductal carcinoma (57%) and invasive lobular carcinoma (36%). In IT treatment, methotrexate was used in 64% of the patients and trastuzumab was used in 36%. Notably, 36% of patients had a partial response, 14% had a stable response, and 50% had disease progression. It was found that approximately 50% of patients with positive cerebrospinal fluid (CSF) cytology became negative after treatment. Furthermore, toxicity of grade 2 or higher was observed in 49% of patients. The median progression-free survival duration among patients who received methotrexate was 1.46 months (95% CI, 0.29–2.0) and among those who received trastuzumab was 5.1 months (95% CI, 0–13.1). The median overall survival duration among all patients was 3.8 months.

LM is an indicator of poor prognosis among patients with breast cancer. However, IT therapy is one of the few treatment options. IT trastuzumab should be considered as a treatment if leptomeningeal metastases develop in HER2-positive breast cancer.

Keywords: Breast cancer, leptomeningeal metastasis, intrathecal therapy, trastuzumab, methotrexate

Introduction

Breast cancer (BC) is the most diagnosed cancer worldwide and is the leading cause of cancer-related death among women (1). Brain metastasis is being increasingly observed in patients with advanced BC, possibly due to improved therapies. A high incidence of brain metastasis is particularly noted in patients with HER2-positive and triple-negative BC (2). Leptomeningeal metastasis (LM), characterized by cancer involvement in the pia, arachnoid mater, and subarachnoid space, occurs in about 5% of metastatic BC cases (3,4).

Patients diagnosed with LM who remain untreated have a poor prognosis with a median overall survival (OS) duration of merely 1 month. Despite contemporary multimodal therapeutic approaches, the median survival of BC patients with LM typically ranges from 2 to 4 months (5). Existing treatments for LM encompass radiotherapy, intrathecal (IT) chemotherapy, systemic therapy, or various combinations of these therapies. Considering the limited ability of systemically administered chemotherapy to penetrate the blood-brain barrier (BBB), IT administration is an effective way of delivering therapeutic agents directly into the subarachnoid space (6). Methotrexate stands out as the most frequently used chemotherapeutic agent for IT therapy in patients with LM; however, its effectiveness is limited (7,8). Hitchins et al. conducted a prospective randomized trial involving 44 patients with LM, including 11 who had BC. In this trial, they administered IT methotrexate or a combination of methotrexate and Ara-C (9). The study reported an overall response rate of 55%. Notably, the response to methotrexate alone was found to be superior compared with the response to the combined therapy. Additionally, seven patients achieved a complete response (CR) (9).

Trastuzumab, when administered intravenously, has a low rate of crossing the BBB, and thus, low levels of trastuzumab are noted in the cerebrospinal fluid

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(CSF). Consequently, some studies have investigated the potential effectiveness of IT trastuzumab treatment in patients with LM (10). A previous retrospective study demonstrated the effectiveness of IT trastuzumab treatment in HER2-positive BC patients with LM (11).

Owing to insufficient data to support the effectiveness of IT therapy, the primary aim of this study was to assess the efficacy and safety of drugs administered intratecaly in BC patients with LM.

Materials and Methods

The study was designed as a single-center retrospective study and was conducted with the permission of Istanbul University Istanbul Faculty of Medicine Scientific Research Evaluation and Ethics Committee (Date:04.03.2021, No:117434). Patients treated at a tertiary oncology center between 2010 and 2022 were included in the study.

Patients were identified from the institution's database, and the study specifically analyzed BC patients with LM who received IT therapy comprising methotrexate and trastuzumab. All patients received IT therapy via an Ommaya reservoir. In each session, CSF samples were initially collected and sent to the laboratory for cytological examination. Methotrexate was administered as an induction therapy at a consistent dose of 10 mg twice a week for 4 weeks, and it was continued until negative results were obtained on cytological examination and clinical improvement was observed. The induction treatment could be extended to a maximum of 8 weeks. After a positive response, maintenance therapy began with weekly doses, and it was eventually converted to monthly administration. IT trastuzumab was initially administered at 50 mg twice a week for 4 weeks, followed by 4 weeks of once weekly doses, and then, maintenance doses were administered every 2 weeks.

Patients whose data were missing for sufficient statistical analysis were not included in the study. Clinical and demographic data, including age at diagnosis, stage, histology, systemic therapy, and local treatments, were retrieved from the medical database.

Treatment responses were evaluated through clinical assessments, cytological examinations (with CSF analysis conducted before each administration until achieving negative results), and radiological scans conducted at regular intervals (approximately every 2–3 months). Following the Response Evaluation Criteria in Solid Tumors guidelines, treatment responses were categorized into the following four groups: CR, partial response (PR), stable disease (SD), and progressive disease (PD). To ensure data accuracy and reliability, patient outcomes were cross-verified with data in the Ministry of Health's death registration system.

Statistical Analysis: Descriptive statistical analyses were performed for all data collected in this study. Survival analysis was performed using the Kaplan–Meier method. OS was defined as the time from the start of IT until death due to any cause. PFS was calculated from the beginning of IT until disease progression or death from any cause. All statistical analyses were performed using SPSS version 25.0, and a P-value of $<.05$ was used to indicate statistical significance.

Results

Characteristics of the Patients and Treatments: In this study contains 14 BC patients who developed with LM. The average age of the patients was 52 (range, 38-64). In terms of pathological characteristics, 8 (57%) patients had invasive ductal carcinoma, 5 (36%) had invasive lobular carcinoma, and 1 (7%) had a different histopathological type. Moreover, among the patients, 12 (86%) showed estrogen receptor positivity, 8 (57%) showed progesterone receptor positivity, and 6 (43%) showed HER2 receptor positivity. Furthermore, 8 (57%) of the patients were concurrently diagnosed with brain parenchymal metastases. Table 1 includes the clinicopathological details of the patients. In terms of perioperative treatment, 13 (93%) patients received chemotherapy and 9 (64%) received adjuvant hormonotherapy. Before undergoing IT therapy, 10 patients (71%) had previously received palliative chemotherapy. Only 1 (7%) patient underwent neurosurgery, and 9 (64%) received brain radiation therapy as local treatment.

Regarding the drugs employed in IT therapy, 9 (64%) patients received methotrexate and 5 (36%) received trastuzumab. In addition to IT therapy, 8 (57%) patients underwent systemic chemotherapy and 2 (14%) received hormonal therapy. Furthermore, 8 (67%) patients had a positive CSF cytology.

Considering treatment responses, 5 (36%) patients achieved PR, 2 (14%) achieved SD, and 7 (50%) experienced disease progression. Notably, CR was not observed in any of the patients. Additionally, 4 (50%) patients achieved a negative CSF cytology, as shown in Table 2.

The average follow-up time after IT treatment was 3 months (range, 1-20 months). Methotrexate-treated

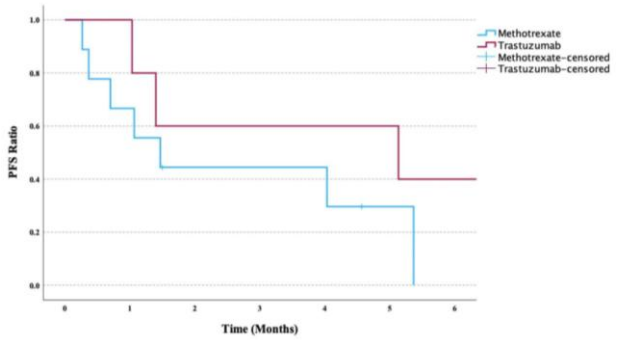

Fig. 1. Kaplan-Meier Curve of Progression Free Survival In Breast Cancer Patients With Leptomeningeal Metastases Treated With Intrathecal Therapy

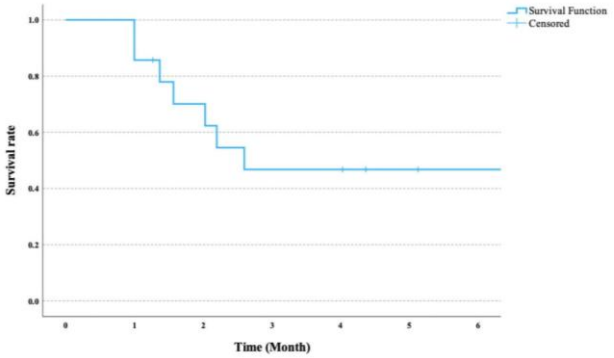

Fig. 2. Kaplan-Meier Curve of Overall Survival In Breast Cancer Patients With Leptomeningeal Metastases Treated With Intrathecal Therapy

patients had a median PFS duration of 1.46 months (95% CI, 0.29–2.0), while trastuzumab-treated patients had a median PFS duration of 5.1 months (95% CI, 0–13.1) (Figure 1). Overall, the median OS duration for all patients was 3.8 months (range, 3.6–11.6 months) (Figure 2).

Among the 14 patients, 2 (14%) exhibited neutropenia of grade 2 or higher, 2 (14%) experienced headaches, and 1 (7%) developed leukoencephalopathy. Mucositis of grade 2 or higher was observed in only 1 (7%) patient. Fortunately, there were no treatment-related deaths among the patients, as indicated in Table 3.

Discussion

BC patients with LM have a poor prognosis and a low OS rate. The therapeutic approach encompasses a multidisciplinary treatment strategy, including IT pharmacotherapy, systemic pharmacotherapy, and radiotherapy. While guidelines endorse the use of IT for treating these patients, its practical application is restricted, primarily due to the requirement for a highly skilled team for administration and the dearth of substantial supporting data in the literature (12).

In a retrospective study by Carausu et al., which encompassed a substantial patient cohort, those with LM who received IT chemotherapy exhibited an OS duration of 4.5 months. Among these patients, 66% received methotrexate as the IT agent. Furthermore, in this study, 10.5% and 55.1% of patients received concurrent radiotherapy and systemic therapy, respectively (13). In a study by Figura et al., the efficacy of three treatment modalities was assessed and compared among 56 patients with LM. These modalities were IT trastuzumab, IT chemotherapy using methotrexate and thiotepa, and whole-brain radiotherapy (WBRT). Notable distinctions in craniospinal PFS were identified, with 6-month rates of 44%, 18%, and 26% observed for IT trastuzumab, IT chemotherapy, and WBRT, respectively. Prolonged disease control, lasting beyond 10 months, was achieved by 4 patients who underwent IT trastuzumab treatment. Furthermore, the 12-month OS rates were 54%, 10%, and 19% (P = 0.01) for trastuzumab, chemotherapy, and WBRT, respectively (14).

A recently published phase II study conducted by Kumthekar et al. involving patients diagnosed with HER2-positive BC with LM, who were treated with IT trastuzumab (totaling 34 patients), reported that 19% of patients achieved PR, 50% achieved SD, and 30% had PD . With a mean follow-up duration of 10.5 months, the study found a median PFS duration of 2.8 months and a median OS duration of 10.5 months (15). A meta-analysis conducted by Zoguiri et al. involved 58 patients, where IT trastuzumab was administered either as monotherapy in 20 patients or in conjunction with systemic chemotherapy in 37 patients. In the study, fifty-five percent of patients experienced significant clinical improvement, while 14% achieved SD. CSF response was noted in 55.6% of patients, and 70.8% showed improvement or stability on magnetic resonance imaging. Median PFS and OS duration after IT trastuzumab treatment were 5.2 and 13.2 months, respectively (16). In a study conducted by Oberkampf et al., which included 19 BC patients diagnosed with LM, PFS and OS durations after IT trastuzumab were 5.9 months and 7.9 months, respectively (17).

Table 1: Clinical and pathological features of the patients

Characteristics		n (%)
Age at diagnosis	<60 years	10 (71)
	≥60 years	4 (29)
Menopause status	Pre-	8 (57)
	Post-	6 (43)
Pathologic subtypes	IDK	8 (57)
	ILK	5 (36)
	Others	1 (7)
Estrogen receptor	Negative	2 (14)
	Positive	12 (86)
Progesteron receptor	Negative	6 (43)
	Positive	8 (57)
HER2-receptor	Negative	8 (57)
	Positive	6 (43)
Stage at diagnosis	Stage 1	1 (7)
	Stage 2	4 (29)
	Stage 3	7 (50)
	Stage 4	2 (14)
AdjuvantRadiotherapy	No	1 (7)
	Yes	13 (93)
Adjuvant chemotherapy	No	1 (7)
	Yes	13(93)
Adjuvant hormone therapy	No	5 (36)
	Yes	9 (64)
Total number of palliative chemotherapy prior to intrathecal treatment	0	4 (29)
	1	2 (14)
	>1	8 (57)
Total number of palliative hormone treatment prior to intrathecal treatment	No	7 (50)
	Yes	7 (50)
Brain surgery	No	13 (93)
	Yes	1 (7)
Brain radiotherapy	No	5 (36)
	Yes	9 (64)
Concomitant parenchymal metastases	No	6 (43)
	Yes	8 (57)
intrathecal treatment agent	Methotrexate	9 (64)
	Trastuzumab	5 (36)
Concomitant systemic therapy	Yok	4 (29)
	Chemoterapy	8 (57)
	Hormonoterapy	2 (14)

In our study, 35.7% of patients achieved PR and 14.3% achieved SD. After treatment, CSF cytology was negative in four patients. The median PFS duration was 1.46 months for patients who received methotrexate and 5.1 months for those who received trastuzumab. The median OS duration for all patients was 3.8 months. On reviewing the mentioned studies, it becomes obvious that while the PFS rates among patients receiving IT (particularly those receiving trastuzumab) were roughly similar to the rates in our study, the OS rates in our study were comparatively lower. We attribute this discrepancy to the relatively small number of patients in our study. Nevertheless, it is noteworthy that the

Table 2: Responses to Intrathecal Therapy For Breast Cancer With Leptomeningeal Metastases

Response ratios	Total n=14 n (%)
Complete response	0 (0)
Partial response	5 (36)
Stable disease	2 (14)
Progression	7 (50.0)
Cytological negativity rate	4 (50)

Table 3: Grade ≥ 2 Side Effects of Intrathecal Therapy

Variables	n (%)
Neutropenia	2 (14)
Leukoencephalopathy	1 (7)
Headache	2 (14)
Vomiting	1 (7)
Mucositis	1 (7)
Treatment-related death	0 (0)

cytological response rate in our study closely aligns with the findings reported in the literature (18).

Generally, IT treatment was well-tolerated, with only 1 patient experiencing severe treatment-related leukoencephalopathy as a notable adverse effect. Other common grade 3–4 side effects included headaches, vomiting, mucositis, and neutropenia. Importantly, there were no treatment-related deaths. These findings align with those reported in prior studies (19).

Limitations of the Study: An important limitation of this study is that it was conducted with a small number of patients. The retrospective design introduced heterogeneity in the patient group and led to some missing data. Additionally, as this was a single-center study, there may have been selection bias.

Considering the poor prognosis of BC patients with LM in terms of mortality and morbidity and the paucity of treatment options for these patients, IT treatment with trastuzumab may be a suitable option, especially in HER2-positive patients. Hopefully, our study's findings, including a positive PFS period, will support this approach and contribute to the literature.

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