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Intrathecal Trastuzumab as a Novel Simplified Therapeutic Strategy for Isolated Metastases in the Leptomeninges in HER2-Positive Breast Cancer: A Case Report and Review of Literature

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Abstract

Leptomeningeal metastases is one of the dreaded complications of metastatic breast cancer, which has a very poor prognosis despite standard treatment, which includes systemic chemotherapy, targeted therapy, and radiation therapy. Intrathecal (IT) therapy has also been used in various studies, which includes IT methotrexate and IT trastuzumab (if the cancer is found to be HER2 +).

We report our experience with the combined modality treatment of systemic chemotherapy with IT trastuzumab in a 52-year-old female patient diagnosed with left breast carcinoma (ER/PR/HER2 status 4/4/3) who progressed in the first year of adjuvant hormonal therapy and developed isolated leptomeningeal metastases. She initially presented with seizures, headache, and neck stiffness. Leptomeningeal enhancement was observed in the magnetic resonance imaging scan of CNS. Positron emission tomography/computed tomography scan showed no evidence of distant metastasis. After confirming cerebrospinal fluid involvement by cytology, the patient was started on IT trastuzumab along with systemic chemotherapy. This resulted in considerable clinical and neurological improvement.

Keywords

- case report
- leptomeningeal metastases
- HER2+ breast cancers
- intrathecal
- trastuzumab

Introduction

Central nervous system (CNS) metastasis occurs in approximately 20% of solid organ cancers of which carcinomas of the lung, breast, and melanoma are the most notorious. It is typically seen in the parenchyma of the brain, but sometimes cancer cells can infrequently infiltrate subarachnoid space, leading to the formation of leptomeningeal metastases.[1] Affected individuals can have a wide spectrum of clinical neurological manifestations like headache, altered sensorium, and neurological weakness because of simultaneous involvement of multiple levels in spinal–cranial neural axis.

Around 6 to 12% patients of HER2+ breast cancers have an isolated leptomeningeal spread and it may be concurrently found in up to 24% of brain parenchyma metastatic breast cancers.[2,3] It is also associated with inferior survival outcomes, with a reported median survival of only 15 weeks.[4] Intrathecal (IT) methotrexate[5–7] and IT trastuzumab[8–10] have been used as part of treatment in such patients. However, the standard of care in our institution for such patients includes radiation therapy and systemic therapy that can include chemotherapy and targeted therapy based on the general fitness of the patients. With this case, we recount our experience on the use of IT trastuzumab for leptomeningeal metastases in a known case of HER2+ breast cancer.

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Case Report

A 52-year-old premenopausal female patient, without any known comorbidities, was diagnosed elsewhere with locally advanced left breast carcinoma. She was referred to us and initially underwent left-sided modified radical mastectomy in January 2023. Postoperative histopathology report was suggestive of mucinous carcinoma: Grade 2, with a pathological stage of pT3N3aM0. Immunohistochemistry revealed ER/PR/HER2 status as 4/4/3 respectively with a Ki-67 of 22%.

She was initiated on adjuvant chemotherapy consisting of four cycles of adriamycin (dose: 60 mg/m^2) and cyclophosphamide (dose: 600 mg/m^2) once in 3-weekly regimen followed by four cycles of paclitaxel (dose: 175 mg/m^2, once in 3-weekly regimen). The patient also received adjuvant radiotherapy (RT) of 40 Gy dose in 15 fractions. She was later put on adjuvant hormonal therapeutic drug tamoxifen from September 2023. She was on regular follow-up since then. She did not receive any HER2-directed treatment as she could not afford this treatment. In October 2024, the patient presented with headache, irritability, and altered behavior for 15 days. Upon evaluation by magnetic resonance imaging (MRI) scan of her CNS, signs suggesting leptomeningeal metastasis were observed: post-contrast subtle enhancement over bilateral cerebellar lobes, bilateral cerebellar foliae at the basal cistern region, with rest of the cerebral parenchyma showing normal signal intensities with no focal lesions. Post the MRI scan, the patient was planned for whole brain RT; however, she developed seizures post three fractions, in view of which RT was deferred.

When the patient was reviewed in the medical oncology outpatient department, she was found to be irritable, disoriented, and with a Glasgow Coma Scale score of 10 ($E_4V_2M_4$). She was initiated on antiepileptics and other supportive measures. Metastatic workup consisted of positron emission tomography/computed tomography, which did not reveal any evidence of distant metastases. Cerebrospinal fluid (CSF) cytology showed the presence of atypical cells, suggesting infiltration by carcinoma. The diagnosis of ER/PR/HER2-positive metastatic breast carcinoma with leptomeningeal metastasis was made.

The patient was started on systemic treatment with Tab. capecitabine 1,250 mg/m^2 twice daily for 14 days in 3-weekly regimen, along with IT trastuzumab administration through Ommaya reservoir. We started her on 20 mg[10] IT trastuzumab twice weekly initially for a period of 4 weeks. However, even this time, our patient did not receive systemic anti-HER2 agents in view of financial constraints. At the end of 4 weeks of biweekly IT trastuzumab administration, we found that the sensorium, cognition, and general performance status of the patient had improved substantially. CSF cytology was repeated, showing clearance of leukemic cells. After six cycles of capecitabine, the patient is planned for hormonal maintenance therapy.

Discussion

Leptomeningeal metastases are one of the dreaded complications of carcinoma breast and the paucity of data on the same makes its treatment challenging. HER2+ breast cancer cells due to their "neurotropism" result in an increased incidence of leptomeningeal spread.[10]

The widely used anti-HER2 agent trastuzumab, an IgG1 antibody, has poor ability to cross the blood–brain barrier (BBB) when administered intravenously. Stemmler et al[11] observed reduced drug concentrations in CSF when trastuzumab was administered intravenously. In patients with intact BBB, the drug concentrations were 420:1, while use of RT allowed more drug to cross the BBB, resulting in CSF concentrations of up to 76:1. This concentration was still below optimal therapeutic levels. Hence, in case of leptomeningeal metastasis, the IT route was tried in some studies.

Lu et al[9] report a case of leptomeningeal disease in a 51-year-old female patient who progressed on systemic trastuzumab therapy. IT administration of the drug improved her condition with overall survival (OS) of up to 46 months since the initiation of the therapy. Similarly, Bousquet et al[8] report a case of leptomeningeal disease in a 34-year-old adult patient where IT trastuzumab was administered with a target to reach CSF concentration of 10 mg/L, and the patient had a progression-free survival (PFS) of 2.5 years. Figura et al,[12] in their retrospective case series consisting of 13 patients, demonstrated that the median time taken from the initiation of IT trastuzumab to disease progression was around 5.7 months and PFS rates at 6 and 12 months are 41 and 21%, respectively. They also reported median survival of 10.6 months and OS rates at 6 and 12 months of 68 and 47%, respectively.

Zagouri et al[13] in their meta-analysis demonstrated that clinical improvement (hazard ratio [HR] = 0.13) and CSF clearance of blasts (HR = 0.13) were associated with longer PFS in CNS.

After 4 weeks of twice-weekly trastuzumab, we found that the sensorium, cognition, and general performance status of the patient had improved notably. CSF Cytology was repeated, showing clearance of leukemic cells.

We would like to highlight the cost-effectiveness of the therapy as the patient who was initially unaffordable for systemic trastuzumab was affordable for IT trastuzumab and the same vial could be used for multiple injections (provided it was discarded at the end of 28 days of reconstitution). This also stresses the fact that IT trastuzumab is a good therapeutic option to patients who cannot afford systemic therapy in CNS disease.

Limitations

The single individual case report of ours will not be sufficient by itself for the generalization of the results and it will be too early to for any conclusion to be made. So, more studies are required to establish the role of single-agent IT trastuzumab conclusively.

Conclusion

This case highlights the effectiveness of IT trastuzumab in leptomeningeal metastatic patients with HER2-positive

breast cancer, as the treatment of choice in combination with systemic chemotherapy, an exceptional option in resource-limited settings. However, further research and clinical trials are needed to refine treatment protocol, establish optimal dosing schedule, and also draw conclusions from the long-term follow-up data.

Author's Contributions

L.K.N.:
Concept: developed the core concept of the case report and provided the overall vision for the manuscript.
Design: led the design of the case report structure and outlined the approach.
Definition of intellectual content: defined the intellectual content, ensuring that the case and its analysis are presented clearly and accurately.
Manuscript preparation: responsible for the initial draft and organization of the manuscript.
A.N.S.:
Concept: contributed to the conceptualization of the case and provided critical insights.
Clinical studies: played a major role in the clinical study aspect, gathering and reviewing the clinical data.
Data acquisition: responsible for collecting the necessary data from clinical records and patient history.
Manuscript preparation: assisted in drafting sections of the manuscript related to clinical findings and interpretation.
B.E.K.:
Design: contributed to the overall structure and design of the manuscript, focusing on the integration of clinical and experimental data.
Data analysis: led the analysis of data presented in the case report, ensuring accuracy and clarity in interpretation.
Statistical analysis: conducted statistical analysis to support the findings and conclusions of the case report.
S.B.:
Literature search: conducted an extensive literature search to support the case report with relevant references and current research.
Manuscript review: assisted in reviewing and proofreading the manuscript for clarity, accuracy, and completeness.
R.A.H.:
Experimental studies: contributed to the experimental data or tests performed as part of the case study.
Data acquisition: helped in the collection of experimental data and clinical observations related to the case.
R.L.K.:
Manuscript editing: participated in editing the manuscript for language, style, and coherence.
Manuscript review: reviewed the manuscript for scientific accuracy and intellectual rigor, ensuring the conclusions are supported by the data.
S.S.:
Clinical studies: contributed to the review of clinical data and assisted in the formulation of the case description.
Manuscript review: played a significant role in reviewing the manuscript and ensuring it adheres to clinical standards.
A.D.P.:
Data acquisition: assisted in gathering data and patient records to support the case report.
Manuscript editing: participated in editing sections of the manuscript to enhance its quality and readability.

Patient's Consent

A written and informed consent was taken from the patient and their kin regarding the publishing of their case summary for educational purposes only. It has also been explained that their patient details are kept anonymous, and identification will be kept confidential.

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None.

Conflict of Interest

None declared.

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