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Case Report

Trastuzumab Deruxtecan for HER2-Positive Breast Cancer with Central Nervous System Metastasis

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Keywords
Brain metastasis · Central nervous system metastasis · Intramedullary spinal cord metastasis · Trastuzumab deruxtecan · HER2-positive breast cancer

Abstract
Introduction: Metastasis to the central nervous system (CNS) is frequently observed in human epidermal growth factor receptor (HER2)-positive breast cancer, leading to reduced quality of life and poor prognosis. Brain metastases (BMs) are common, whereas spinal cord metastases are rare and no standardized treatment approach has been reported for their management. Herein, we report the outcomes of treatment with trastuzumab deruxtecan (T-DXd) in a patient with BMs and intramedullary spinal cord metastasis (ISCM) and another patient with BMs. ***Case Presentation:*** The first patient was a woman in her 30s. After the surgery for HER2-positive right breast cancer, T-DXd was used as fourth-line treatment for multiple BMs and ISCM. Both the BMs and ISCM reduced, and partial response was maintained for 12 months. Grade 1 fatigue was the only adverse event observed in this patient. The second patient was a woman in her 40 s with multiple BMs after primary treatment for HER2-positive right breast cancer, as well as multiple bone and lymphoid node metastases. T-DXd was administered as second-line treatment. The multiple BMs have now shrunk, and the primary tumor and bone/lymph node metastases have not shown significant changes; the patient has maintained partial response for 6 months. ***Conclusion:*** Metastasis to the CNS has a very poor prognosis and limited therapeutic response because it is difficult for drugs to cross the blood-brain barrier. However, T-DXd has yielded positive results for BMs in clinical trials. Additionally, a therapeutic effect of T-DXd on ISCM and BMs was observed in the reported cases.

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Introduction

Brain metastases (BMs) occur in 30–50% of human epidermal growth factor receptor 2 (HER2)-positive breast cancer cases [1], worsening the prognosis and quality of life of patients. This poor prognosis may be attributed to the blood-brain barrier (BBB), which is a highly selective diffusion barrier that limits the entry of toxins and drugs into the brain, making the delivery of therapeutic agents to the central nervous system (CNS) challenging [2]. Although BMs can impair the BBB and increase its permeability, most drugs do not reach therapeutic levels in the brain [3]. Therefore, local interventions, such as surgery and radiotherapy, are the primary treatment modalities for BMs, whereas systemic treatment is considered an adjunctive option [4]. In contrast, the use of anti-HER2 agents improves the prognosis in patients with HER2-positive breast cancer and BMs, while systemic pharmacotherapy, including anti-HER2 agents, can be considered a treatment option for patients with HER2-positive breast cancer [5].

In contrast, intramedullary spinal cord metastasis (ISCM) is rare; it is present in approximately 2% of autopsy cases and clinically detected in 8.5% of cancer cases with CNS metastases [6]. Although the prognosis of patients with advanced breast cancer has improved owing to advances in treatment, CNS metastases have been on the rise over the past 2 decades [7]. Additionally, the incidence of ISCM may also increase in the future, which is concerning as its management lacks a standardized treatment approach. Trastuzumab deruxtecan (T-DXd) has been shown to be effective in the treatment of breast cancer with BMs [4]. Meanwhile, T-DXd for breast cancer with ISCM has not yet been reported. Herein, we report 2 cases of breast cancer with BM and ISCM treated with T-DXd.

Case Presentation

Case 1

A 37-year-old woman with right breast cancer underwent total right mastectomy and sentinel node biopsy and was diagnosed with estrogen receptor-positive, progesterone receptor positive, and HER2-immunohistochemistry 3+ right breast cancer T1c, N0, M0, stage IA according to the 8th International Union Against Cancer (Fig. 1a, b) [8]. In June 2014, the patient was administered four cycles of trastuzumab (Tmab) (6 mg/kg, day 1) + docetaxel (75 mg/m^2, day 1) every 3 weeks; four cycles of fluorouracil, epirubicin, and cyclophosphamide (500 mg, 100 mg, and 500 mg/m^2, day 1) every 3 weeks; and 14 cycles of Tmab (6 mg/kg, day 1) every 3 weeks + tamoxifen (20 mg/day). The patient developed liver and multiple bone metastases 2 years after surgery while receiving tamoxifen (20 mg/day). Consequently, she was administered Tmab (6 mg/kg, day 1) + pertuzumab (Pmab) (420 mg/body, day 1) + docetaxel (75 mg/m^2, day 1) every 3 weeks as the first-line treatment for 16 months from October 2016. Due to multiple bone metastases (spine and skull), second-line treatment with trastuzumab emtansine (T-DM1) (3.6 mg/kg, day 1) every 3 weeks was initiated in March 2018. Despite the administration of 28 cycles of T-DM1, the appearance of pituitary metastasis with bilateral hemianopsia was observed 5 years postoperatively. Therefore, Tmab (6 mg/kg, day 1) + Pmab (420 mg, day 1) + eribulin (1.4 mg/m^2, days 1 and 8) every 3 weeks (eribulin was omitted after the 9th cycle) were administered as third-line therapy after gamma knife of 16 Gy for pituitary metastasis from January 2020. However, multiple BMs (right frontal, temporal, and occipital lobes) and ISCM (C7, Th12, L1, and L4) were detected on contrast computed tomography (CT) (Fig. 2a, b). Finally, T-DXd (5.4 mg/kg, day 1) every 3 weeks commenced as fourth-line treatment post-18 Gy gamma knife treatment in February 2021. CT performed 2 months after T-DXd

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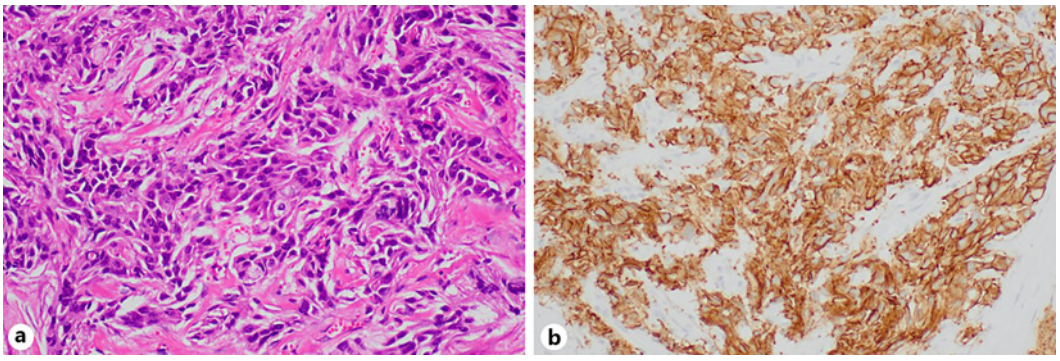

Fig. 1. Histopathological examination and IHC of specimen from right breast cancer **a** Solid tubular carcinoma with intraductal spread (hematoxylin and eosin, *200). **b** Anti-HER2 staining indicates HER2-strong positive expression (*200). HER2, human epidermal growth factor receptor 2.

treatment showed shrinkage of the brain and spinal cord metastases (Fig. 2c, d). CT after 53 courses of T-DXd showed that the BMs continued to diminish, and spinal cord metastases were difficult to detect. Consequently, the patient maintained partial response (PR) to T-DXd. Grade 1 fatigue according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) was the only adverse event observed, and the patient has been on continuous T-DXd therapy since.

Case 2

A 41-year-old woman was diagnosed with right breast cancer and multiple bone and lymph node metastases and was diagnosed with estrogen receptor-negative, progesterone receptor-negative, HER2-immunohistochemistry 3+, and cT1c, N3, M1 (OSS, LYM), c stage IV right breast cancer according to the 8th International Union Against Cancer [8] in the previous hospital she had visited. Magnetic resonance imaging (MRI) performed at the previous hospital revealed no BMs. Primary treatment with Tmab (6 mg/kg, day 1) + Pmab (420 mg/body, day 1) + docetaxel (75 mg/m^2, day 1) every 3 weeks was administered at the previous hospital from August 2022; following reduction in the primary tumor size and lymph node shrinkage, the patient was deemed to have PR. After 10 cycles of primary treatment, the patient was transferred to our hospital on account of proximity. Routine head MRI performed at our facility revealed numerous high-signal nodules in the cerebellum, and multiple cerebellar metastases (Fig. 3a), while a CT examination revealed that the primary tumor had reduced in size, and lymph node metastasis had almost disappeared (Fig. 3b). No abnormal neurological signs were observed. Thus, the patient was determined to have progressive disease. Whole-brain radiation therapy (WBRT; 35 Gy in 14 fractions) was performed for multiple BMs. Second-line treatment with T-DXd was initiated (5.4 mg/kg, day 1) every 3 weeks in June 2023. Grade 2 anorexia was observed, which improved after the second course with increased dose of olanzapine (5.0 mg/day, day 2–7). After the second course of T-DXd, cerebellar metastases were hardly perceptible on head MRI (Fig. 3c); the primary lesion in the right mammary gland did not appreciably change on CT (Fig. 3d), and the metastatic axillary lymph node remained reduced in size. Thus, the patient was determined to have PR. Although olanzapine was discontinued after the sixth course, the patient continued to experience grade 1 anorexia. Currently, the patient is being treated with 17 cycles of T-DXd and is maintaining PR. The observed adverse events include anorexia, diarrhea, and peripheral neuropathy (all grade 1) according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

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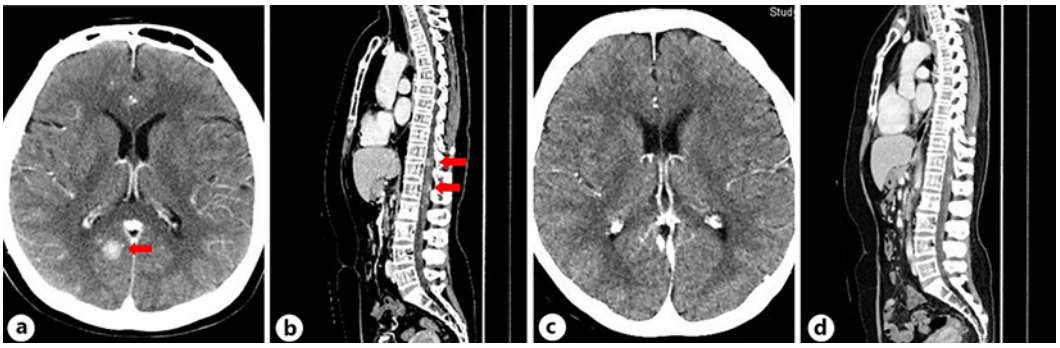

Fig. 2. Contrast CT. **a** A tumor with contrast effect was found in the right occipital lobe, and BM was confirmed on CT before gamma knife therapy and T-DXd administration (red arrows). **b** The spinal cord at the level of thoracic vertebra 12, lumbar vertebra 1, and lumbar vertebra 4 showed areas of contrasted lesions, and spinal metastasis was confirmed on contrasted CT before gamma knife therapy and T-DXd administration (red arrows). **c** CT scan at 10 months after the commencement of T-DXd shows shrinkage of the BMs and edematous changes in the surrounding tissues. **d** On CT scan obtained 10 months after the commencement of T-DXd, spinal cord metastases are difficult to detect. CT, computed tomography; T-DXd, trastuzumab deruxtecan.

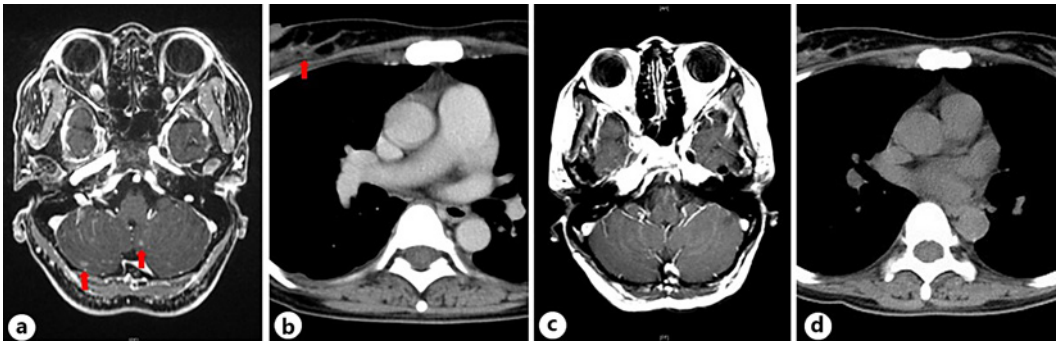

Fig. 3. CT and MRI before and after T-DXd treatment. **a** T1-weighted MRI of the head showed multiple high-signal nodules in the cerebellum, and a diagnosis of cerebellar metastasis was made (red arrows). **b** On CT, the primary lesion in the right mammary gland had shrunk compared to the size at the initial treatment (red arrow). **c** Contrast-enhanced MRI after the second course of T-DXd shows that the intensely nodular areas in the cerebellum have shrunk and are difficult to identify. **d** On CT, the primary right breast cancer site showed no change in size. CT, computed tomography; MRI, magnetic resonance imaging; T-DXd, trastuzumab deruxtecan.

Discussion

Here, we reported two cases of advanced breast cancer with CNS metastases that responded to T-DXd. Patients with HER2-positive breast cancer have a higher incidence of CNS metastasis than those with HER2-negative cancer, with approximately one-fourth of patients with metastases developing CNS disease [9]. Although CNS metastasis has a strong negative impact on the quality of life, treatment options for advanced or recurrent HER2-positive breast cancer are rapidly advancing, with the development of anti-HER2 agents, such as antibody-drug conjugates and tyrosine kinase inhibitors.

T-DXd is the antibody-drug conjugate of the monoclonal anti-HER2 antibody and topoisomerase I inhibitor [10]. It is reportedly effective against not only HER2-positive

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breast cancer but also HER2-low breast cancer, and it is widely used in breast cancer treatment [11]. It is also widely used in breast cancer cases with metastasis, with positive outcomes being reported. Several clinical studies have been conducted on T-DXd in patients with breast cancer and BMs. A summary study of T-DXd outcomes for breast cancer with BMs in 17 cases reported an objective response rate of 73% for CNS lesions [12]. Additionally, the study suggested that HER2-positive BMs in other diseases may be targeted with T-DXd [12]. In another report, the 12-month overall survival and objective response rates were reported to be 81% vs. 66% and 54% vs. 69% in patients with BMs and those with extracranial lesions alone, respectively, with comparable outcomes for T-DXd in both patient groups [13]. Although the benefits of T-DXd for BMs have been reported, the prognostic factors have not yet been clearly elucidated. The DESTINY-Breast04 trial evaluated the safety and efficacy of T-DXd in HER-negative advanced breast cancer [11]. It included 32 patients (5.7%) with BMs. The progression-free survival in the hormone receptor-positive group was 10.1 months in the T-DXd arm versus 5.4 months in the physician's choice arm; the median overall survival in the hormone receptor-positive group was 23.9 months in the T-DXd arm and 17.5 months in the physician's choice arm.

Originally, HER2-targeting drugs achieved therapeutic effects in proportion to HER2 expression; however, the efficacy of T-DXd may be independent of the HER2 expression level. Other reports have suggested that the damage caused by radiotherapy or tumor invasion into the CNS may trigger the passage of T-DXd through the BBB [14]. Thus, the presence of CNS metastases or prior radiotherapy may be a prognostic factor for T-DXd treatment. Nevertheless, further studies are warranted to explore these prognostic factors in greater detail.

With prolonged cancer survival, the chances of encountering ISCM are expected to increase. Lung cancer is the most common primary site (54%) of ISCM, followed by breast cancer (13%) [14]. Standard treatment for ISCM is yet to be established. Early resection of the primary lesion in patients with paralytic symptoms improves the symptoms in 77% of the cases [15]. However, the efficacy or survival advantage of chemotherapy for patients with ISCM has not been reported [15]. Since the cases we reported had no paralytic symptoms, T-DXd treatment was initiated without surgery, and the spinal cord metastases disappeared on imaging. Nevertheless, no studies have reported T-DXd treatment for patients with cancer who have ISCM. Thus, although T-DXd has accumulating benefits for the CNS, its efficacy for the treatment of ISCM remains to be fully evaluated. Further research is required in this regard as this study is a case study and cannot contribute to evidence accumulation.

Side effects should be carefully considered when administering T-DXd. In particular, deaths due to interstitial lung disease have been reported (5 cases, 2.7%) [16]; hence, it is important to evaluate krebs von den lungen (KL-6) before use, to interview the patient during administration, and perform routine radiological examinations or CT examination. In the two reported cases, routine blood examination and CT examinations were performed and no obvious signs of interstitial lung disease were observed. Routine examinations should be carried out while using T-DXd in the future.

The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542761).

In conclusion, our findings suggest that T-DXd may be effective in managing CNS metastasis (BMs and ISCM).

Statement of Ethics

Ethics approval was not required in accordance with local guidelines for this retrospective unplanned study. Written informed consent was obtained from the patient for treatment and for the publication and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.Y. wrote the draft and critically revised the manuscript for important intellectual content. H.Y., T.I. and K.K. contributed to the conception of the work. T.I. and K.K. diagnosed and treated this patient. H.Y. confirmed the authenticity of the raw data. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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