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Dose-reduced trastuzumab deruxtecan can be safely used in liver failure and active leptomeningeal metastases

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Abstract

Trastuzumab deruxtecan has been shown to have responses in heavily pretreated patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. However, the safety of this medication in patients with severe liver dysfunction and untreated or symptomatic central nervous system metastases is unknown. We describe a patient with metastatic HER2-positive breast cancer with liver failure and leptomeningeal metastases who was treated with dose-reduced trastuzumab deruxtecan. With treatment, the patient's hyperbilirubinemia resolved and she demonstrated a response on imaging. She was dose-escalated to full dose with minimal adverse events.

Keywords

Metastatic breast cancer; HER2; Antibody-drug conjugate; Liver failure; Leptomeningeal metastases

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CRediT authorship contribution statement

Nicole Higashiyama: Conceptualization, Writing - original draft, Writing - review & editing. **Julie Nangia:** Writing - review & editing. **Maryam Nemati Shafaee:** Writing - review & editing. **Nan Chen:** Writing - review & editing. **Binu Liz Michael:** Writing - review & editing. **Mothaffar Rimawi:** Writing - review & editing. **Valentina Hoyos:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Patient consent statement

Written, informed consent for this publication was obtained from the patient.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Introduction

Trastuzumab deruxtecan is an anti-HER2 humanized monoclonal antibody conjugated to a topoisomerase I inhibitor. In December 2019, the U.S. Food and Drug Administration (FDA) issued an accelerated approval for its use for the treatment of unresectable or metastatic HER2-positive breast cancer (mHER2+BC) after two or more anti-HER2-based regimens. This approval was granted based on the results of the DESTINY-Breast01 trial, an open-label, single-group, multicenter, phase 2 study showing a 60.9% overall response rate including 11 (6%) complete responses and a 16.4 month median progression-free survival in heavily pretreated patients (median 6 prior lines of therapy, including trastuzumab emtansine) with unresectable or mHER2+BC (Modi et al., 2020). These results are encouraging for patients with mHER2+BC, and trastuzumab deruxtecan has quickly been added to our anti-HER2 targeted treatment armamentarium. However, the role of trastuzumab deruxtecan in individuals with severe liver dysfunction or untreated or symptomatic central nervous system metastases (CNSm) is unclear since these patients were excluded from the study. Inclusion was limited to those with previously treated, stable CNSm and moderate hepatic dysfunction (total bilirubin ≤ 3 g/dL and aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 5 times the upper limit of normal) (Modi et al., 2020). Thus, whether the administration of trastuzumab deruxtecan is safe in patients outside these parameters is unknown. This question is especially pertinent considering that 30–50% of mHER2+BC patients have or will develop brain metastases (Brufsky et al., 2011; Hurvitz et al., 2019; Pestalozzi et al., 2013) and 25–30% have liver involvement at initial metastatic presentation (Wu et al., 2017; Kennecke et al., 2010).

Here we describe the case of a patient with both untreated leptomeningeal metastases and liver failure due to progressing liver metastases, who was treated with trastuzumab deruxtecan without significant toxicity and with an ongoing response to treatment, including normalization of her liver function tests and resolution of areas of leptomeningeal involvement.

Case report

A 45 year-old woman with estrogen receptor positive, progesterone receptor positive, HER2 positive (by fluorescent in situ hybridization), grade 3 invasive ductal carcinoma of the breast with metastases to the liver, bones, lymph nodes, pachymeninges, and leptomeninges, presented to the hospital in January 2020 with leg pain, right upper quadrant abdominal pain, and headache. At the time, she was being treated with trastuzumab, pertuzumab, goserelin, and exemestane. She had 4 lines of therapy previously including goserelin, letrozole, trastuzumab, and pertuzumab for 17 months; trastuzumab emtansine, goserelin, and letrozole for 2 months; capecitabine and lapatinib for 10 months; and docetaxel, trastuzumab, and pertuzumab for 4 months. She had also previously received radiation (3000 cGy in 10 fractions) to the bilateral mandibles for symptomatic inferior alveolar nerve involvement, as well as stereotactic radiosurgery (2700 cGy in 3 fractions) to a right parasagittal dural mass.

Work-up for the abdominal and leg pain revealed stable bony metastases, but enlarging left axillary lymphadenopathy and multiple bilateral small pulmonary nodules. The hepatic metastases appeared stable on imaging. However, the liver appeared cirrhotic and she had acute cholestatic liver dysfunction (total bilirubin 2.5 mg/dL, alkaline phosphatase 620 U/L, ALT 51 U/L, and AST 216 U/L). Magnetic resonance cholangiopancreatography showed no evidence of obstruction. Hepatitis studies were negative. Exemestane was held due to concerns for cholestatic liver injury (LiverTox 2012) and she was discharged with follow-up.

She was re-admitted in February for anxiety and uncontrolled cancer-related pain. This time, her total bilirubin worsened to 3.8 mg/dL and her Eastern Cooperative Oncology Group performance status had declined to 3, so hospice was considered. However, the decision was made to reassess her treatment candidacy as an outpatient.

After discharge, her total bilirubin continued to rise to 6.6 mg/dL with an alkaline phosphatase of 1188 U/L, AST of 250 U/L, and ALT of 42 U/L. Since she had been off exemestane for over four weeks, it was suspected that some degree of her liver dysfunction was attributable to worsened liver metastases. Brain imaging showed an increased 2.1 × 3.5 × 1.2 cm right occipitotemporal dural-based metastasis projecting into the leptomeninges, a new 1.1 × 0.9 cm dural-based metastasis along the parietal interhemispheric fissure, and mild increase in a right occipital calvarial metastasis (Fig. 1 A and 1 B). Radiation to these sites was considered, but with her worsening liver failure and improvement in her performance status to 2 with adequate pain control, the decision was made to treat her systemically. No lumbar puncture was performed for cerebral spinal fluid analysis prior to treatment since the imaging was highly suggestive of leptomeningeal involvement, she was rapidly deteriorating, and there were logistical constraints in obtaining a lumbar puncture in a timely manner. She was started on trastuzumab deruxtecan with a 25% dose-reduction (4 mg/kg). No next generation sequencing was available at this time to suggest other systemic treatment options.

By cycle 1 day 17, the patient's leg pain resolved, bilirubin improved to 2.2 mg/dL, and performance status improved to 1. Imaging on cycle 2 day 6 showed a positive response with a 0.7 cm decrease in the left axillary lymphadenopathy and resolution of the pulmonary nodules. There was further improvement in the left axillary lymphadenopathy and hepatic metastases on imaging obtained after cycle 3. Additionally, the hyperbilirubinemia resolved (Fig. 2). Therefore, the patient's treatment was escalated to full-dose trastuzumab deruxtecan. After 7 months of therapy, her disease continues to respond clinically with stable hepatic metastases on imaging after cycle 9 (Fig. 3) and reduced pain medication requirement. She has also shown near resolution of the dural metastases with no evidence of leptomeningeal and decreased pachymeningeal enhancement (Fig. 1 C and 1 D). Her only side effects have been a mild infusion reaction with cycle 1, asymptomatic grade 3 hypoproliferative anemia after cycle 1 with negative work-up for hemolysis or bleed, and worsening of her baseline anxiety requiring a serotonin-norepinephrine reuptake inhibitor.

Discussion

In the past year, the FDA has approved three new agents, trastuzumab deruxtecan, tucatinib, and neratinib, for the third-line treatment of patients with mHER2+BC, significantly increasing our therapeutic options in this poor prognosis setting. With the remarkable responses seen in the DESTINY-Breast01 trial, it will be necessary to determine the sequence of therapies that offers the most benefit to patients. This is particularly important in those who develop CNS and liver metastases, since they are associated with meaningful morbidity and mortality (Lee et al., 2008; Eichbaum et al., 2006). Moreover, they prove challenging, as not all drugs can penetrate the blood brain barrier and liver dysfunction limits our therapeutic options due to the high risk of toxicity.

CNSm occur in up to 30–50% of mHER2+BC patients (Brufsky et al., 2011; Hurvitz et al., 2019; Pestalozzi et al., 2013). The mainstay of treatment has been surgery or radiation, which are associated with significant morbidity. Small molecule tyrosine kinase inhibitors lapatinib, neratinib, and tucatinib have the strongest evidence of CNS penetration and activity against CNSm with overall responses in combination with capecitabine between 30 and 65% (Murthy et al., 2020; Bachelot et al., 2013; Petrelli et al., 2017; Freedman et al., 2019). Therefore, these are the preferred systemic treatments in patients with active CNSm. However, in patients with concurrent high burden of systemic disease and visceral crisis (as was the case of our patient), probabilities of rapid systemic response are more promising with trastuzumab deruxtecan, making the decision between the two options challenging.

The role of anti-HER2 antibody-drug conjugates in treating CNSm is not established. Given their large molecular size, they have poor CNS penetration. However, studies have demonstrated that CNSm disrupt the blood brain barrier, which may contribute to some drug penetration (Lockman et al., 2010). Additionally, case series and retrospective studies have shown activity of the antibody-drug conjugate trastuzumab emtansine in CNSm, with response rates as high as 24–30% (Kalsi et al., 2015; Keith et al., 2016; Fabi et al., 2018; Bartsch et al., 2015). Thus far, trastuzumab deruxtecan has not been studied in untreated CNSm. The DESTINY-Breast01 trial included individuals with previously treated, stable CNSm and we eagerly await the full details on CNSm responses seen in this study (Jerusalem et al., 2020).

After 5 cycles of trastuzumab deruxtecan, our patient had near resolution of her leptomeningeal involvement from a dural-based metastasis. It is possible that in this patient, the proximity of the metastasis to the blood brain barrier caused disruption to allow for drug penetration. Whether the same benefit of trastuzumab deruxtecan can be seen in parenchymal brain metastases warrants further investigation. Regardless, the ongoing response seen in our patient is remarkable given the particularly poor prognosis observed with leptomeningeal disease with a median survival of approximately 4 months (Franzoi and Hortobagyi, 2019).

In addition to leptomeningeal metastases, our patient exhibited a high burden of liver metastases with a cirrhotic appearance on imaging and liver failure. Hepatic dysfunction caused by liver metastases significantly limits our therapeutic options. Despite this,

trastuzumab emtansine has been used in this setting with some evidence of benefit (Sharp and Johnston, 2015). However, which patients will benefit is unpredictable, since trastuzumab emtansine itself can cause severe hepatotoxicity (Diéras et al., 2013). Specifically, cases of liver failure and death have been associated with the development of nodular regenerative hyperplasia (Diéras et al., 2013).

Transaminitis has been reported as a trastuzumab deruxtecan adverse effect. However, grade 3 or 4 AST elevations were only seen in 2% of patients (Modi et al., 2020) compared to 4.3% with trastuzumab emtansine (Verma et al., 2012). Though they are both antibody-drug conjugates, mouse models suggest that the hepatotoxicity of trastuzumab emtansine results from emtansine-associated intracellular damage of HER2 expressing hepatocytes due to upregulation of TNFα and apoptosis (Yan et al., 2015). Since trastuzumab deruxtecan is linked to a topoisomerase I inhibitor rather than a microtubule inhibitor, it remains to be seen whether a similar type of hepatotoxicity may occur. Irinotecan, another toposisomerase I inhibitor, has been associated with steatohepatitis, but not nodular regenerative hyperplasia (Robinson et al., 2012). This is the first reported use of trastuzumab deruxtecan in a patient with significant liver failure (Child-Pugh Class B). With treatment, her bilirubin normalized, indicating this might be the best choice of therapy for patients in this dire situation.

Conclusion

Here we described a patient with mHER2+BC with liver failure and previously untreated leptomeningeal metastases who was safely treated with dose-reduced trastuzumab deruxtecan as fifth-line therapy. The patient's hyperbilirubinemia resolved rapidly, enabling escalation to full-dose with minimal adverse events. She achieved both a significant systemic and CNS response. Therefore, the use of dose-reduced trastuzumab deruxtecan in severe liver dysfunction and in patients with leptomeningeal carcinomatosis should be investigated in prospective trials.

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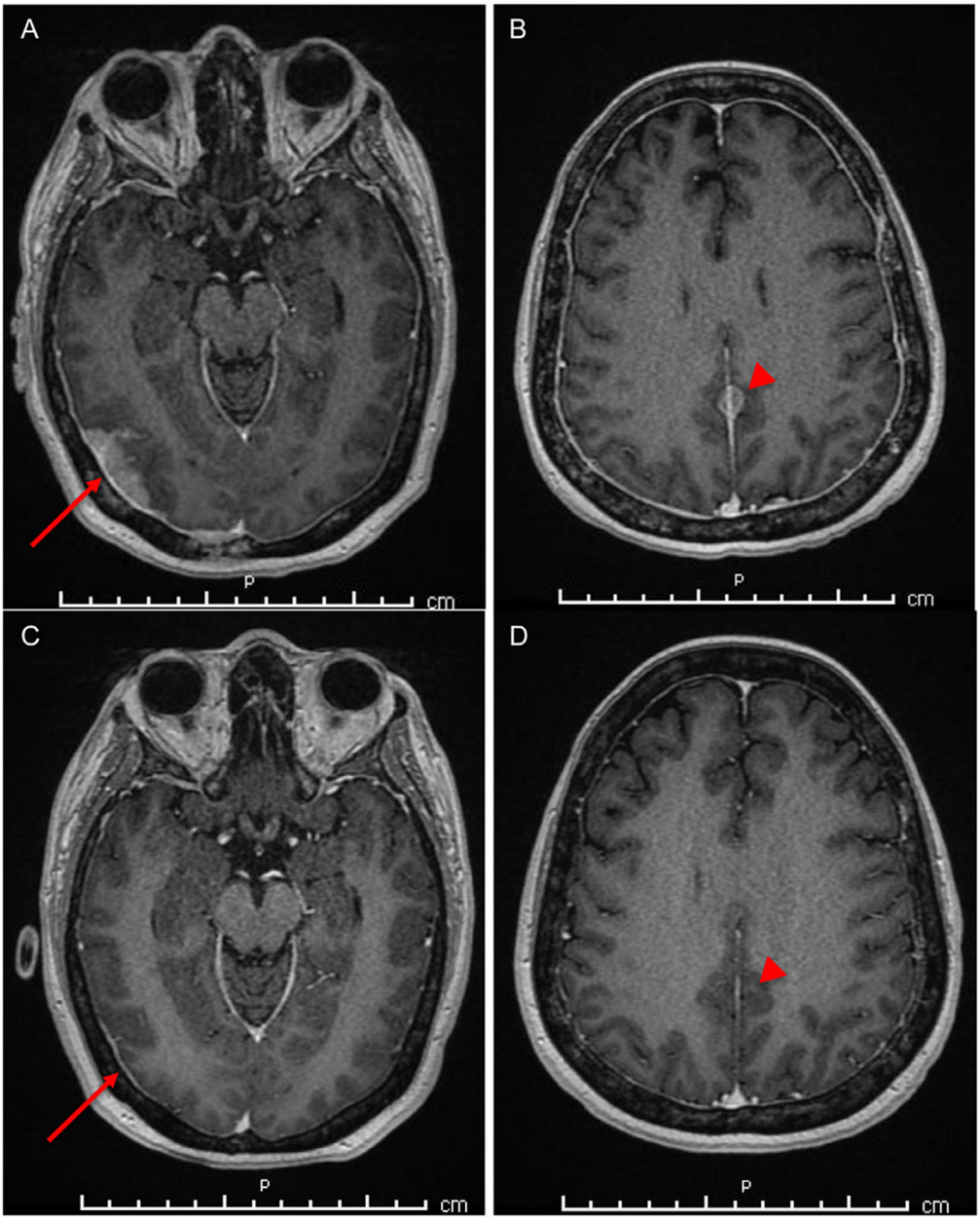

Fig. 1.

Axial 3D brain volume (BRAVO) T1-weighted post-contrast brain magnetic resonance image (MRI) at baseline before trastuzumab deruxtecan treatment (A, B) and after 9 cycles of trastuzumab deruxtecan (C,D). **(A)**, A 2.1 × 3.5 × 1.2 cm right occipitotemporal dural-based metastasis with projection into the leptomeninges and associated vasogenic edema (indicated by red arrow). **(B)**, A 1.1 × 0.9 cm dural-based metastasis along the parietal interhemispheric fissure (indicated by red arrowhead). **(C)**, Near resolution of the right occipitotemporal dural-based metastasis with leptomeningeal involvement. **(D)**, Resolution of the dural-based metastasis along the parietal interhemispheric fissure.

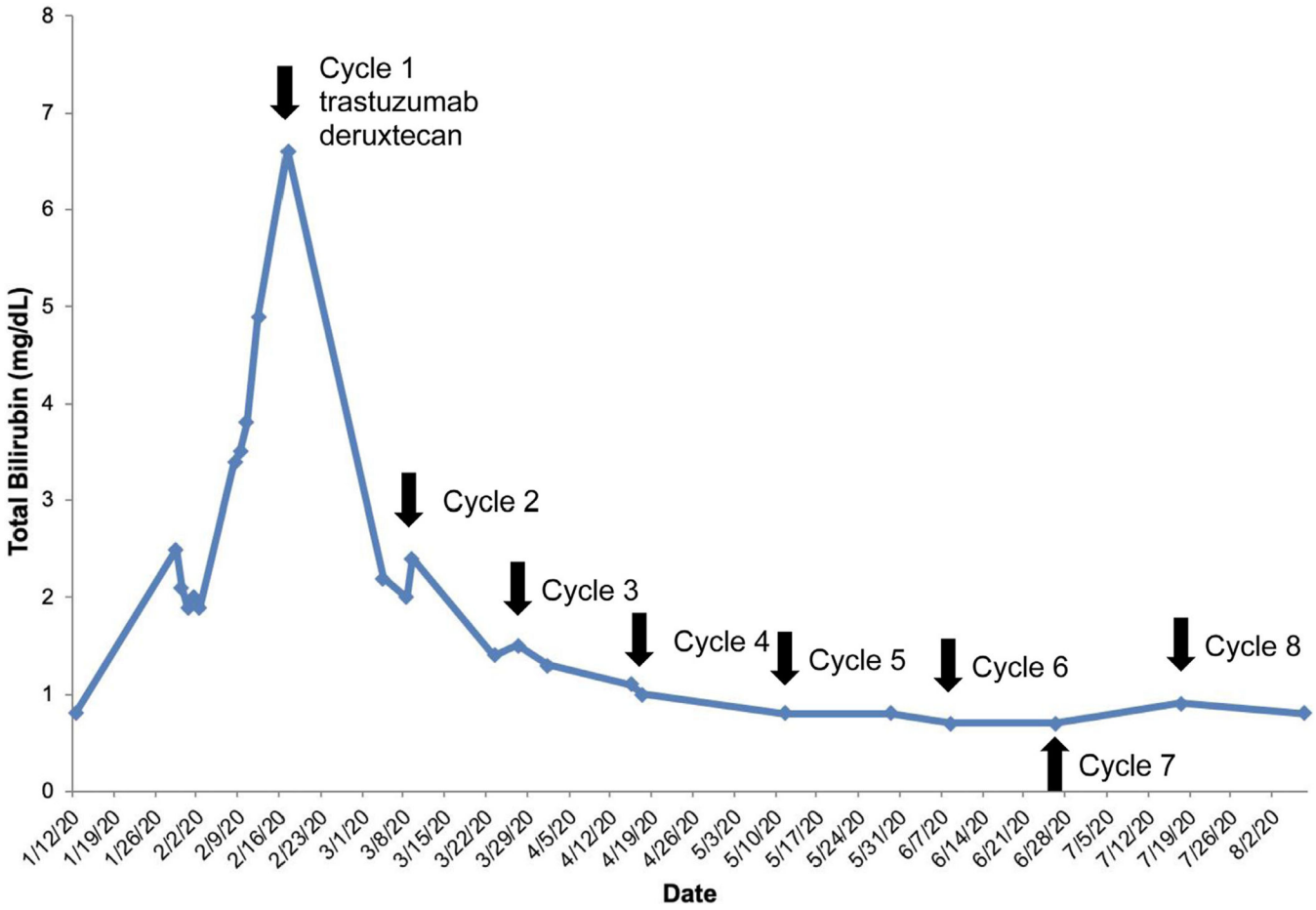

Fig. 2.
Total bilirubin levels during treatment with trastuzumab deruxtecan.

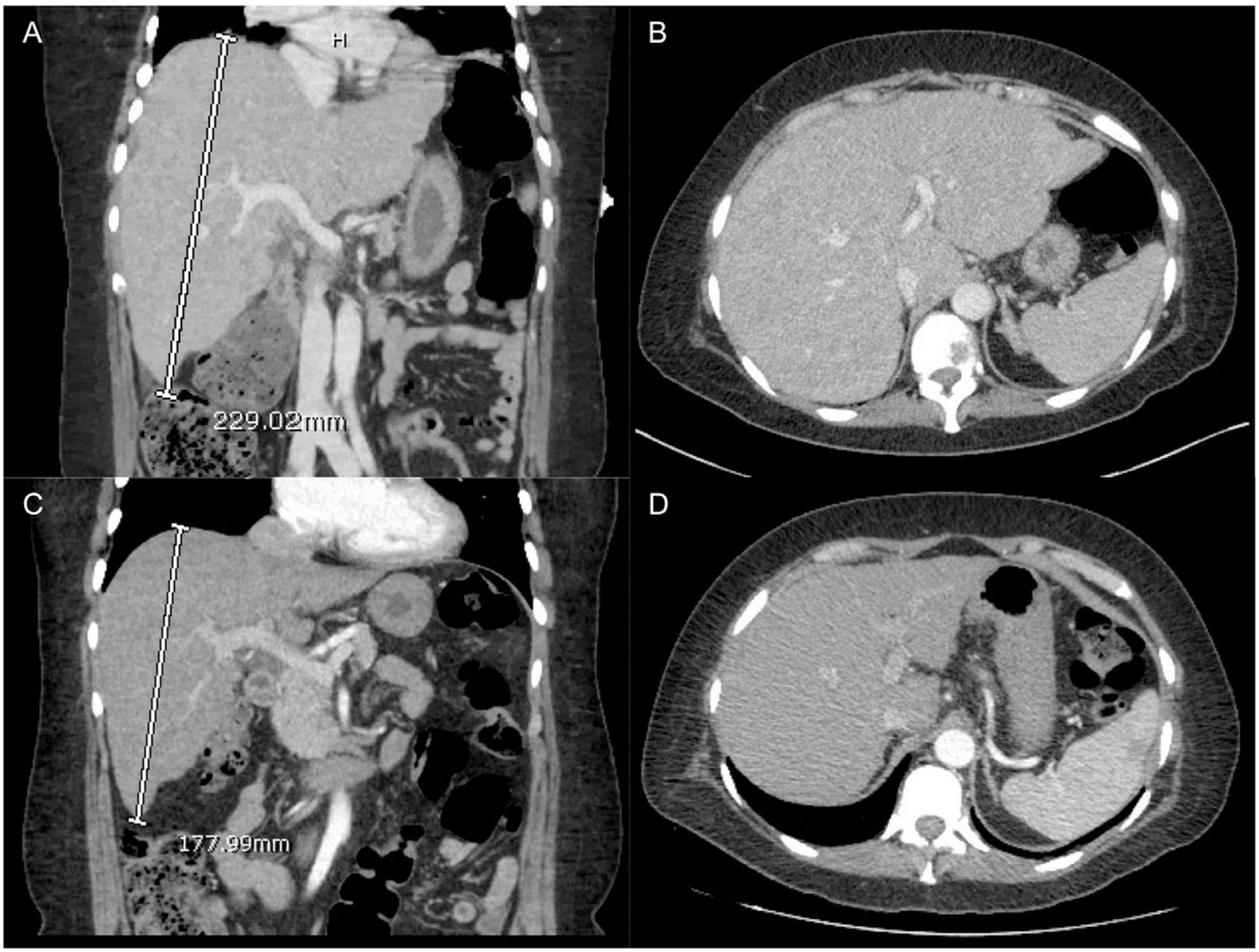

Fig. 3.

Computed tomography of the liver with contrast at baseline before trastuzumab deruxtecan treatment (A, B) and after 9 cycles of trastuzumab deruxtecan (C, D). **(A)**, Coronal view demonstrating a nodular liver contour and hepatomegaly with multiple subcentimeter hypoattenuating metastases throughout. **(B)**, Axial view demonstrating multiple hypoattenuating liver lesions. **(C)**, Coronal view demonstrating nodular contour but reduced hepatomegaly and less conspicuous hepatic metastases. **(D)**, Axial view demonstrating decreased hepatic metastases.