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**LETTERS TO THE EDITOR**

# Ado-trastuzamab emtansine associated hyponatremia and intracranial hemorrhage

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**To the Editor,**

Ado-trastuzamab emtansine (T-DM1) is an antibody-drug conjugate (ADC) approved for the second-line treatment of HER2-positive (HER2+) metastatic breast cancer. This agent is in clinical trials for use in first-line metastatic disease, adjuvant and neoadjuvant treatment due to the superior efficacy with reduced toxicity demonstrated in the pivotal trial [1]. The mechanisms of action involve binding of the monoclonal antibody to HER2 on the cell surface to inhibit HER2 receptor signaling, HER2 shedding and triggering of the antibody-dependent cell-mediated cytotoxicity (ADCC) immune response. Once bound, the compound is internalized via endocytosis and is degraded inside the tumor to release emtansine or DM1, which binds to microtubules and inhibits polymerization causing cell-cycle arrest and death [2–4].

The most common adverse drug reactions (ADR) in early clinical trials of T-DM1 were nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and constipation [1]. Additionally, hepatoxicity, cardiotoxicity with reductions in left ventricular ejection fractions, interstitial lung disease including pneumonitis, infusion-related reactions, and peripheral neuropathy was reported [5]. Recently, Roche released a Direct Healthcare Professional Communication about severe hemorrhage in patients receiving T-DM1 advising caution in patients with thrombocytopenia.

A recent report [6] describes a radiation recall phenomenon with increased brain edema in patients treated with T-DM1 having previous stereotactic radiosurgery. This study described edema and necrosis at tumor sites that was posited to be due to enhanced cell death and inflammation elicited by T-DM1 in HER2 upregulated glial cells at the edematous sites. Here we describe a case involving previously irradiated brain metastasis of HER2+ cancer leading to both hyponatremia and intracranial hemorrhage despite an adequate platelet count after T-DM1 treatment.

A patient with a 13-year history of metastatic breast cancer to lung and bone and three-year history of brain metastases initiated treatment with T-DM1 3.6 mg/kg given every 21 days. Complications requiring hospitalization occurred a total of three times over six cycles. She had previously been treated with ovarian suppression, tamoxifen, vinorelbine and trastuzumab, exemestane, whole brain irradiation (external beam intensity modulated radiotherapy 39.8 Gy in 1.8 Gy/fraction, 3 years prior to T-DM1), capecitabine and lapatinib, stereotactic radiosurgery (8 lesions were treated with 1750 cGy per lesion using 11 isocenters, 2 years prior to T-DM1), and trastuzumab and lapatinib prior to initiating T-DM1.

The patient was first admitted one week after the first treatment of ado-trastuzamab for increasing episodes of partial seizures and confusion. Laboratory results upon arrival showed a sodium level of 118 mmol/L (previous week's baseline was 131 mmol/L). The hyponatremia was treated with normal saline, which raised her sodium level. The cause of the hyponatremia was thought to be mainly poor oral intake and dehydration with cerebral salt wasting. Dexamethasone was started to decrease cerebral edema, thought to be most likely related to necrotic

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metastatic foci. A multisequence, multiaxial magnetic resonance imaging (MRI) of the brain showed mild increase in edema surrounding the right temporal lobe convexity region and the right occipital lobe, but otherwise no significant changes in remaining intracranial metastatic lesions.

After the second infusion with T-DM1 the patient was again taken to the emergency room with complaints of confusion, feeling unsteady, and decreased oral intake. Her laboratory reports showed a low serum sodium concentration of 118 mmol/L, low serum chloride concentration at 91 mmol/L, low serum inorganic phosphorous of 2.3 mg/dL and low serum osmolality at 243 mOsm/kg. Additionally, urine osmolality was 537 mOsm/kg while urine sodium concentration was 116 mmol/L. Serum sodium rose to a stable range of 124–126 mmol/L from intravenous fluid during hospitalization. Patient was discharged on free water restriction and demeclocycline. She remained mildly hyponatremic (133–134 mmol/L) for the next three months. Four more cycles of T-DM1 progressed without further hospitalizations.

Two days prior to the scheduled seventh cycle, the patient was admitted to the emergency room after a generalized tonic-clonic seizure. A computed tomography (CT) of the head demonstrated an interval acute hemorrhage in the metastastic lesion at the posterior left parietal high convexity without significant mass effect. The patient was not on any anti-coagulant or anti-platelet agents at the time of the final hospitalization. Her platelet level was 132 000/mm$^3$.

After being informed of treatment options, the patient and her family elected to pursue hospice. She was discharged home with hospice and died shortly thereafter.

## Discussion

In breast cancer there is a 30% incidence of intracranial metastases at autopsy [7]. While intracranial hemorrhage rates are unknown for this subtype, having a HER2 + positive tumor predisposes to brain metastases [8–11].

In November 2013, Genentech released an addendum to current safety information including severe hemorrhage in patients with fatal outcomes including central nervous system bleeding. Caution when treating patients who develop thrombocytopenia and avoidance of anti-coagulation therapy and anti-platelet agents are advised [12, 13]. However, our patient had only a mild thrombocytopenia from the treatment.

She did have symptomatic brain metastases treated three years prior to T-DM1 treatment with whole brain radiotherapy, capecitabine and labatinib, and reoccurrence at former central nervous system (CNS) sites two years prior to T-DM1 treatment which were treated with stereotactic radiosurgery.

The development of hyponatremia after beginning treatment with T-DM1 is a potentially complicating aspect to the case. However, increased brain edema manifesting within 1–2 weeks of T-DM1 treatment has been recently reported in patients with previous stereotactic radiosurgery [6]. The patients in that report also demonstrated headaches, nausea, vomiting, memory deficits, gait disturbance and visual changes similar to our patient. Assessment of sodium status was not described. Our patient had evidence of necrosis and increased edema on the MRI performed after her first T-DM1 treatment for her first hospitalization for hyponatremia. It is plausible that T-DM1 elicited a tumor response in the previously irradiated brain metastases resulting in inflammation and edema that resulted in a cerebral salt wasting effect causing the hyponatremia. Imaging was not repeated to assess edema or necrosis after her second treatment. The concurrent findings of the prior report and our patient suggest an enhanced inflammatory effect after T-DM1 treatment at previously irradiated brain metastases that may result in localized brain injury and explain the development of hemorrhage in our patient. This may represent a cancer treatment response since our patient had no evidence of progression of her disease at the time of hemorrhage.

It is reasonable to closely monitor patients with known brain metastases during treatment with T-DM1 for hyponatremia and evidence of hemorrhage.

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