

**LETTER TO THE EDITOR****To THE EDITOR****Intrathecal Trastuzumab as a Potential Cause of Drug-Induced Aseptic Meningitis**

**Keywords:** Intrathecal chemotherapy, Breast cancer, Leptomeningeal carcinomatosis

Breast cancer is the commonest cause of leptomeningeal carcinomatosis (LC). The prognosis of LC remains dismal, since overall survival reaches 6 months.<sup>1</sup> HER-2 is a transmembrane tyrosine kinase receptor belonging to the epidermal growth factor receptor family and is overexpressed in approximately 20% of breast cancers. Trastuzumab emtansine is a humanized monoclonal IgG1 antibody-drug conjugate made up of trastuzumab, inhibitor of the HER2, stably linked to a highly potent chemotherapy, emtansine, and its role as a systemic therapy for metastatic HER2-positive breast cancer is well established.<sup>2</sup> Its high molecular weight does not allow penetration through the blood-brain barrier.<sup>3</sup>

We report the case of a 36-year-old woman diagnosed on March 2012 with metastatic left breast adenocarcinoma, infiltrating, HER-2 positive. On May 2015, after two courses of trastuzumab emtansine, radiologic progressive disease with diffuse leptomeningeal enhancement was diagnosed and the patient was eligible for Herceptin intrathecal (“HIT”) study, NCT01373710.<sup>4</sup> This is a prospective study aiming to analyze the impact of intrathecal (IT) trastuzumab 150 mg weekly during 8 weeks and its antitumor activity in terms of neurological progression-free survival at 2 months. The first five injections were perfectly well tolerated. A day after the IT administration of the fifth course, the patient presented at the emergency department with severe headache, neck stiffness, and photophobia. Blood analysis was normal. The cerebrospinal fluid (CSF) protein level was elevated (1.49 g/L), the CSF glucose was reduced, and WBC count was equal to 4500 cells/μl (98% neutrophils). Broad spectrum antibiotic therapy was initiated (cefotaxime and vancomycin) after CSF analysis. Serum C-reactive protein levels were elevated on day 2 but decreased on subsequent blood tests. Initially, a brain CT was performed that did not show any significant modification and after 5 days a brain MRI showed a stable disease. Gram stains and cultures of CSF were negative, so antibiotic therapy was discontinued on day 5 and CSF analysis was normal at day 7.

We determined that the patient had suffered a drug-induced aseptic meningitis, secondary to IT trastuzumab administration. The complete resolution of drug-induced aseptic meningitis led us to the decision to continue treatment. On day 8, the patient received the sixth course of IT trastuzumab, with no adverse events. CSF study revealed an elevated WBC count, equal to 74 cells/μl and normal protein levels.

We therefore present a case of aseptic meningitis incited by the IT administration of trastuzumab as part of a successful treatment for leptomeningeal disease. Since excellent disease control was achieved, assessed by radiologic response and normal neurologic examination, it was decided not to discontinue

IT treatment. The regimen was discontinued on January 2016, after 15 courses of IT trastuzumab, because of radiological progression of cerebromeningeal lesions. The patient’s survival is remarkably long, reaching 61 months since the first diagnosis of LC. At last evaluation, on November 2018, there were no signs of progressive disease.

Drug-induced aseptic meningitis is an uncommon, probably under-reported entity.<sup>5</sup> Neutrophilic prevalence and normal-to-low CSF glucose in the CSF study, as in our patient, are reported in the majority of cases in the literature.<sup>5</sup> A causative link with intravenous monoclonal antibodies has been reported<sup>5</sup> as well as with other IT chemotherapies.<sup>6</sup> Interestingly, we found another case of drug-induced aseptic meningitis attributed to IT trastuzumab.<sup>7</sup> However, in the previous case, it was decided to stop IT trastuzumab and the patient suffered progressive neurologic decline.<sup>7</sup> Remarkably, both cases have a similar drug-induced aseptic meningitis potentially associated with IT trastuzumab. However, we decided to resume the treatment due to the risk-benefit ratio and the lack of other therapeutic alternatives. Clinicians must be aware of the potential association between IT trastuzumab administration and drug-induced aseptic meningitis because rechallenge is possible due to its potential therapeutic benefit.

Breast cancer is the leading cause of LC and neurotropism is a common feature of breast tumors presenting with HER-2 overexpression. It is important for clinicians to be aware of any potential complication of IT trastuzumab, in order not to unnecessarily discontinue this promising therapy.

**CONFLICT OF INTEREST**

The authors have declared no conflicts of interest.

*Evangelia Pappa*

*AP-HP, Hôpitaux Universitaires Pitié Salpêtrière – Charles Foix, Service de Neurologie 2-Mazarin, Paris F-75013, France*

*Rosa Conforti*

*AP-HP, Hôpitaux Universitaires Pitié Salpêtrière – Charles Foix, Service d’Oncologie, Paris F-75013, France*

*Khê Hoang-Xuan and Agusti Alentorn*

*AP-HP, Hôpitaux Universitaires Pitié Salpêtrière – Charles Foix, Service de Neurologie 2-Mazarin, Paris F-75013, France*

*Inserm U 1127, CNRS UMR 7225, Institut du Cerveau et de la Moelle épinière, ICM, Sorbonne Universités, UPMC, University Paris 06, UMR S 1127, Paris F-75013, France*

*Correspondence to:* Agusti Alentorn, Service de Neurologie-2, Hôpitaux Universitaires Pitié-Salpêtrière, 46-83 Boulevard de l’Hôpital, Paris F-75013. Email: [agusti.alentorn@aphp.fr](mailto:agusti.alentorn@aphp.fr)

## REFERENCES

1. Nayar G, Ejikeme T, Chongsathidkiet P, et al. Leptomeningeal disease: current diagnostic and therapeutic strategies. *Oncotarget*. 2017;8:73312–28.
2. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659–72.
3. Kordbacheh T, Law WY, Smith IE. Sanctuary site leptomeningeal metastases in HER-2 positive breast cancer: a review in the era of trastuzumab. *Breast*. 2016;26:54–8.
4. Bonneau C, Paintaud G, Trédan O, et al. Phase I feasibility study for intrathecal administration of trastuzumab in patients with HER2 positive breast carcinomatous meningitis. *Eur J Cancer*. 2018; 95:75–84.
5. Morís G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis revisited. *JAMA Intern Med*. 2014;174: 1511–2.
6. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: a retrospective case series. *J Neurooncol*. 2012; 109:143–8.
7. Freyer CW, Yaghmour G, Jennings K, et al. Drug-induced aseptic meningitis associated with intrathecal trastuzumab. *J Pharm Technol*. 2014;30:43–7.