

# **CASE REPORT : A SEVERE INFUSION REACTION DURING THE FIRST DOSE OF INTRAVENOUSLY ADMINISTERED TRASTUZUMAB**

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## **Abstract**

**Objective:** To report a case of severe infusion reaction during the first dose of intravenously administered trastuzumab.

**Methods and Results:** Here we present a case of a 53-year-old female patient (V. Y) with HER 2 positive breast cancer who, after completion of primary therapy (mastectomy, radiotherapy and chemotherapy) has developed hepatic and thoracic vertebrae metastatic formations. Due to this, the staff recommended trastuzumab (Herceptin) and capecitabine (Xeloda) for six months, but during the intravenously administered trastuzumab, the patient developed a severe infusion reaction manifested with hypertension (175/98 mm Hg), shortness of breath, cyanosis, pounding heart, panic attack, chills and fever. Trastuzumab is not associated with the adverse events that typically occur with chemotherapy, such as alopecia, myelosuppression, and severe nausea and vomiting. With the exception of hypersensitivity, which has been seen mainly and occasionally with the first infusion, cardiotoxicity (principally congestive heart failure) is the most important adverse effect of trastuzumab.

**Conclusions:** Investigations of trastuzumab in the adjuvant setting require careful patient monitoring and stopping rules specified for hypersensitivity reactions and cardiotoxicity.

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**Keywords:** Trastuzumab, HER 2 positive breast cancer, infusion reaction.

## **Background**

Trastuzumab (Herceptin, Roche), a humanized monoclonal antibody against the extracellular domain of HER2, has been shown to benefit patients with HER2-positive metastatic breast cancer. Vogel, Cobleigh, Tripathy, et al (2002) and Baselga, Carbonell, Castaneda-Soto NJ, et al (2005) reported that trastuzumab is safe and efficacious when administered weekly or every three weeks, alone. After a phase III, multinational, randomized controlled trial, Slamon, Leyland-Jones, Shak, et al (2001), and after a randomized phase II trial, Marty, Cignetti, Maraninchi, et al (2005) reconfirmed its efficacy and safety even in combination with chemotherapy. According to Bell (2002), trastuzumab is not associated with the adverse events that typically occur with chemotherapy, such as alopecia, myelosuppression, and severe nausea and vomiting. In prescribing information of Genentech Inc. (2005), the most important adverse effect of trastuzumab is cardiotoxicity (principally congestive heart failure), whereas hypersensitivity has been seen mainly and occasionally with the first infusion. For this reason, investigations of trastuzumab in the adjuvant setting require careful patient monitoring and stopping rules specified for hypersensitivity reactions and cardiotoxicity.

Hereby we present a case of a female patient with breast cancer disease who, after completion of primary therapy (mastectomy, radiotherapy and chemotherapy) has developed hepatic and thoracic vertebrae metastatic formations, as well as a severe hypersensitivity reaction during the first dose of intravenously administered trastuzumab.

## **Case report**

In May 2013, a 53-year-old female patient (V. Y) with record number of 174, showed up at oncology service of UHC “Mother Teresa” in Tirana with a mass in the left breast. She was recommended routine laboratory and imagery studies. Findings were as follows: a 4 cm nodule with irregular borders in left breast (superior-lateral quadrant) and left axillary lymph nodes of 1.5 cm; on breast sonography; a 4.5 cm nodule with irregular borders and micro calcifications in left breast (superior-lateral quadrant) on mammography; a C5 fine needle aspiration (FNA) cytology; normal X-ray of thorax and abdomen ultrasound; normal tumor markers (CEA, Ca 15-3). In her history of life, the patient reported two normal deliveries, one abortion, normal lactation (one year for each child) and no hormonal administrations. She also reported being allergic to penicillin and taking medications for hypertension.

The patient had left mastectomy at axillary lymph node dissection-Modificate Madden, and a good postoperative outcome. Histopathologic examination reported: ductal infiltrative carcinoma with an lobular

infiltrative component of grade 2 and carcinomatous metastasis in 14 of 16 examined lymph nodes, pT<sub>2</sub>, N<sub>3</sub>, Mx. Immuno-histochemical examination for hormonal receptors and prognostic markers concluded: ER = 1 %, Pr = 5 %, HER-2/*neu* = 3 + and Ki = 67 20 %. The final diagnosis was: left breast cancer, T<sub>2</sub>, N<sub>3</sub>, M<sub>0</sub>; she was recommended to a chemo- and radiotherapist for further treatment. The medical staff opted for chemotherapy regimen (administered as adjuvant treatment postoperatively) 4 AC/ 4 T, plus radiotherapy and endocrine therapy (tamoxifen), which has been initiated in June 2013.

After four cycles of chemotherapy, in September 2013, the check-up ultrasonography results were: no focal lesions on left thoracic site of mastectomy; benign nodule on right breast 6 x 4 mm without axillary adenopathy; one 9 mm granulomatous calcification in liver, without evidence of secondary formations. Laboratory analysis showed adequate baseline, hepatic, renal, and bone marrow function. The staff recommended to continue on four cycles with taxane and radiation therapy.

Besides taxane and radiation therapy, in February 2014, the patient initiated endocrine therapy Nolvadex (tamoxifen 20 mg tab.). Five months later, in July 2014, the patient came back to hospital complaining of back and shoulder pain. Skeletal scintigraphy detected metastasis in thoracic vertebrae T<sub>3</sub>-T<sub>7</sub>, which constituted indication for palliative analgesic radiotherapy. She was also given Bondronat (ibandronic acid 50 mg tab.).

Three months later the control ultrasonography results were: clear right and left thoracic quadrants; no axillary and supraclavicular adenopathy; hepatic steatosis, 3-4 hypoechogenic lesions of 15 mm diameter. CT confirmed hepatic metastasis and osteolytic lesions on thoracic vertebrae. Laboratory analysis detected: CEA = 20. 19 (normal < 6. 5 ng/ml), Ca 15-3 = 334.8 (normal < 25U/ml) and ALP = 1450 (normal < 270 U/l). The staff recommended trastuzumab (Herceptin) and capecitabine (Xeloda) for six months.

Before initiating trastuzumab the patient underwent a transthoracic echocardiography with the following results: mild diastolic dysfunction with left ventricular ejection fraction (LVEF) 0. 59 (normal > 0. 55). Because of allergic to penicillin, before administering trastuzumab the patient was given diphenhydramine and acetaminophen. Within two minutes of infusion the patient developed a severe infusion reaction manifested with hypertension (175/98 mm Hg), shortness of breath, cyanosis, pounding heart, panic attack, chills and fever. She was given oxygen, diazepam 5 mg/ ml (1 amp), CaCl<sub>2</sub> 10 % (2 amp), prednisolone 25 mg/ml (3 amp), dexamethazone 4 mg/ml (2 amp) and furosemid 10 mg/ml (1 amp). She was stable one hour later. Due to this event, the staff had to decide an alternative approach for the next future.

In November 2014, the patient initiated another treatment regimen with capecitabine, and is doing well with it.

## **Discussion**

Yarden and Sliwkowski (2001), as well as Gschwind, Fischer and Ullrich (2004) demonstrated that *HER2/neu* (hereafter referred to as *HER2*) belongs to a family of four transmembrane receptor tyrosine kinases that mediate the growth, differentiation, and survival of cells. According to Slamon, Godolphin, Jones, et al. (1989), overexpression of the *HER2* protein, amplification of the *HER2* gene, or both occur in approximately 15 to 25 percent of breast cancers, and are associated with aggressive behavior in the tumor. The use of trastuzumab is associated with the risks of severe and rarely fatal infusion-related reactions (e.g., bronchospasm, dyspnea, hypoxia, severe hypotension) generally with the first dose (possibly during or immediately following the infusion (Hellmann, 2000, Section, Cautions for Herceptin, ¶ 6). In those with acute signs and symptoms the initial improvement may be followed by marked clinical deterioration leading to further complications. Severe infusion-related reactions may result in death within hours of the infusion or up to 1 week after the infusion. On the other hand, subsequent infusions may be tolerated following complete recovery, typically accompanied by prophylactic treatment (e.g., antihistamines and/or corticosteroids); severe reactions may recur despite the use of premedication.

## **Conclusion**

The most important adverse effect of trastuzumab are cardiotoxicity and hypersensitivity reactions. Infusion must be interrupted in patients who develop dyspnea or clinically important hypotension. Patients should be monitored until signs and symptoms of these effects completely resolve. Discontinuance of trastuzumab should be strongly considered in patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome (ARDS).

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