

Successful readministration of trastuzumab after severe immune reactions in two breast cancer patients

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Summary Trastuzumab is a standard treatment in breast cancer overexpressing Her2 oncogene. However, its administration carries the risk of severe immune adverse events which often lead to the discontinuation of trastuzumab. There is no clear guideline on how patients experiencing trastuzumab-related reaction should be rechallenged with the monoclonal antibody. Here, we present two case reports of patients who have presented severe anaphylactic reactions during trastuzumab infusion. Both of them have been successfully rechallenged in intensive care units with premedication, lower rate of infusion and vitals monitoring. Thereafter, trastuzumab could be continued without any serious adverse reaction. Given the positive impact of trastuzumab on patients' survival, treatment rechallenge should be carefully considered in patients who presented anaphylactic reactions.

Keywords Trastuzumab · Rechallenge · Metastatic breast cancer · Anaphylaxis

Background

Monoclonal antibody trastuzumab is commonly used to treat patients with positive HER2 breast cancer offering a

significantly longer median time to disease progression, a higher overall response rate (ORR), a longer median duration of response as well as a longer survival time [1].

However, about 40 % of patients receiving trastuzumab are expected to experience mild immune reactions during the first infusion alone [2]. A small percentage will present more serious reactions [3]. To date, there is no clear guideline on whether those patients should be rechallenged with trastuzumab, or which process to adopt to do so [2, 4].

In the present report, we briefly describe two cases of successful trastuzumab rechallenge in patients with metastatic breast cancer who had already experienced trastuzumab-related anaphylactic reactions.

Report

Patient #1, 53 year-old, had been diagnosed with metastatic breast cancer in May 2013. Due to suspicion of thrombotic micro-angiopathy, she initially received weekly infusions of doxorubicine until the definitive anatomopathological report, which showed HER2 overexpression. The hospital staff decided to change her treatment. She then started receiving a loading dose of trastuzumab 4 mg/kg along with weekly paclitaxel 80 mg/kg.

Patient #2, 40 year-old, was receiving her sixth infusion of weekly trastuzumab 2 mg/kg combined with paclitaxel 80 mg/kg as first line therapy for a metastatic breast cancer.

During their trastuzumab infusion, both patients developed an anaphylactic shock requiring treatment with methylprednisolone, dexchlorpheniramine, inhalation of ipratropium, as well as intravenous fluid, associated in both cases with favorable response. In both patients, the trastuzumab treatment was discontinued.

After a multidisciplinary meeting, it was decided to rechallenge patients with trastuzumab (patient #2 having

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experienced progression while receiving lapatinib plus capecitabine as second line). The rechallenge of the drug was performed in Intensive Care Unit. Patients were premedicated, with methylprednisolone, dexchlorpheniramine and ranitidine. Patient #1 as well as patient #2 received a 4 mg/kg trastuzumab over 3 h and 5 h respectively (instead of 90 min) and were monitored for blood pressure, heart rate and oxygen saturation for 24 h. Indeed, there was no sign of anaphylaxis observed during or after the administration of trastuzumab combined with paclitaxel. The following infusions were delivered at the same rate of infusion and premedication, without any adverse event either.

Discussion

About 40 % of trastuzumab-treated patients develop infusion-related reactions, most often during the first infusion [2]. About 1–3 % will experience more serious immune reactions [3], and for those patients there are no guidelines or recommendations concerning trastuzumab rechallenge. The current recommendation of the manufacturer is to permanently discontinue trastuzumab treatment in patients who previously developed anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome [3]. If the drug is not replaceable, desensitization may be recommended. This strategy has not yet been validated and infusion reaction may still happen during the desensitization process [4].

Acute reactions following infusion of monoclonal antibodies can be caused by various mechanisms, including acute anaphylactic and anaphylactoid reactions against the monoclonal antibodies, serum sickness, tumor lysis syndrome and cytokine release syndrome. The clinical manifestation can range from local skin reactions at the injection site, pyrexia and an influenza-like syndrome, to potentially fatal acute anaphylaxis accompanied with systemic inflammatory response syndrome [5].

The exact mechanism responsible for infusion reactions to monoclonal antibodies is still undetermined. Theoretically, infusion reactions to chimeric and humanized monoclonal antibodies may be a result of their ability to elicit human antichimeric antibodies and human anti-human antibodies, respectively [6]. However, the correlation between infusion reactions and these antibodies has not yet been demonstrated. The fact that most infusion reactions happen during the first infusion suggests that prior sensitization may not be required. While some IgE against monoclonal antibodies have been proven to exist prior to any infusion of antibodies, these reactions are unlikely to be true such as type I IgE-mediated

hypersensitivity reactions [7, 8]. Similar reactions can be caused by non IgE mediated basophiles activation or by cytokine release.

Trastuzumab is standard care in Her2+ breast cancer treatment. The alternate treatments have been less studied (e.g. lapatinib) and may cross-react (e.g. TDM-1). As such, the discontinuation of trastuzumab is an important decision that should be carefully discussed, as it results in a poorer disease prognosis. Trastuzumab rechallenge may be discussed in multidisciplinary council in case of a potential anaphylactic reaction. Patients should be premedicated and closely monitored during the first rechallenge and infusion rate should in fact be decreased. In our experience, trastuzumab rechallenge was performed successfully through lower rate infusion and premedication by anti-histaminics and corticoids. As a result, there was no symptom of anaphylactic reaction during the following infusions [2]. These clinical experiences are consistent with other data on hypersensitivity reactions, suggesting that such early reactions can be minimized or avoided by ensuring appropriate premedication and cautious rate of infusion [4].

The mechanism responsible for the reaction as well as the criteria for a rechallenge should both be studied in further depth.

Conflict of interest The authors declare that they have no conflict of interest.

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