Evaluation of a Human Fab Anti-Idiotypic Anti-Daratumumab to Resolve Pan Reactions in Pre-Transfusion Testing due to Monoclonal Anti-CD38 Therapy

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Background

Monoclonal antibody therapies are used to treat a variety of pathologic conditions including solid and hematologic cancers. Daratumumab, a monoclonal anti-CD38 antibody, has been used for several years and has been shown to be efficient for the treatment of multiple myeloma patients. This monoclonal antibody specifically targets the antigen CD38, which is overexpressed on multiple myeloma cells. However, CD38 is also expressed in various degrees on red blood cells. When a patient is treated with daratumumab, pan reactions are observed in antibody screening using the Indirect Antiglobulin Test (IAT), which may mask underlying clinically significant antibodies. Several solutions have been developed, such as soluble recombinant proteins or treating the reagent red blood cells with dithiothreitol or trypsin, but they present limitations in the detection of some red cell alloantibodies.

Aims

The objective of this study was to confirm, in two different immunohematology laboratories, the efficacy of a new candidate in neutralizing daratumumab interferences in pre-transfusion testing. Another objective was to demonstrate that this candidate has no impact on the detection of underlying red cell antibodies.

Methods

The neutralizing solution was provided ready-to-use. The daratumumab relative concentration in patient samples was estimated by antibody titration. To assess the neutralization efficiency, 50 daratumumab samples (25 samples per site) were titrated and neutralized starting with 10% v/v of neutralizing solution and then with an increasing concentration if the neutralization was not achieved at 10% (i.e., 20% and then 30% v/v of neutralizing solution). No preincubation was required. Thereafter, 40 samples (20 samples per site) were prepared with a weak alloantibody (titer equal to or smaller than 4 against single dose cell) and daratumumab at a known titer. Specificities were selected to represent a broad spectrum of clinically significant antibodies. These positive samples were tested using the same neutralization protocol starting with 10% and so on if needed. Respective dilution controls using a titration buffer at 10%, 20% or 30% were used at each step to validate the neutralization tests.

Results

At both sites, daratumumab titers ranged between 8 to 16,384. Overall, 74% of the samples (37/50) were neutralized using 10% of anti-daratumumab: all samples up to a titer of 1024 (19/19), 80% with a titer of 2048 (4/5), 86% with a titer of 4096 (12/14), 22% with a titer of 8192 (2/9) and none with a titer of 16,384 (0/3). At both sites, 92% (46/50) neutralization was achieved with 20% and then 100% with 30%. All underlying clinically significant alloantibodies were detected after the efficient neutralization of daratumumab. Of 40 positive samples, 38 (95%) were neutralized with 10% and 2 required 20% of anti-daratumumab, but it did not affect the detection of weak underlying antibodies. Two samples showed positive but weaker reactions with 10% anti-daratumumab but eventually gave expected reactivities on subsequent testing.

Summary / Conclusions:

This human Fab anti-idiotypic anti-daratumumab demonstrated very efficient neutralization while allowing for the detection of weak underlying red cell antibodies. Using a 10% concentration, the neutralization was successful in 83% of samples (75/90), and gradual increase achieved a complete neutralization. This user-friendly reagent could become a new candidate for daratumumab neutralization in pre-transfusion testing.

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