NHS
Blood and Transplant

Therapeutic monoclonal antibodies & blood transfusion

Essential information for hospital transfusion laboratories, transfusion practitioners & haematology clinical teams

March 2018

Caring Expert Quality

NHS
Blood and Transplant

Background

- Targeted therapeutic monoclonal antibodies are used to treat patients with myeloma and other haematological malignancies.
- It is likely that these patients will need regular transfusion support.
- Depending on the nature of the monoclonal antibody, these drugs may interfere with pre-transfusion testing.
- The use of these targeted monoclonal antibody therapies is increasing, as promising clinical trials lead to their administration in routine clinical practice.

NHS
Blood and Transplant

Which drugs are involved?

- Anti-CD38 (Daratumumab ▼ for multiple myeloma)
  - NICE technology appraisal, due to complete March 2018. The use of this drug is likely to increase.

There are other drugs currently undergoing trials and you may also encounter these:

- Anti-CD47 (CAMELLIA for acute myeloid leukaemia and myelodysplastic syndrome)
  - Trial due to complete August 2018
- Anti-CD38 (Isatuximab for multiple myeloma)
  - Trial due to complete May 2019
  - Currently collecting data on interference with testing. Follow protocol for Daratumumab patients.

▼ this medicinal product is subject to additional monitoring

NHS
Blood and Transplant

CAMELLIA overview

- CAMELLIA (anti-CD47) is a monoclonal antibody used to treat acute myeloid leukaemia and myelodysplastic syndrome.
- CD47 is widely expressed on human tissues and red cells.
- CD47 acts as a marker of self, a "Do not eat me" signal for healthy tissue.
- Blocking of CD47 on the surface of Red blood cell (RBC) with the use of targeted monoclonal antibodies decreases the protective signal and increases the phagocytosis of circulating RBCs by macrophages in the spleen.
- Increased phagocytosis by splenic macrophages is clinically manifested with indices of extravascular haemolysis.

NHS
Blood and Transplant

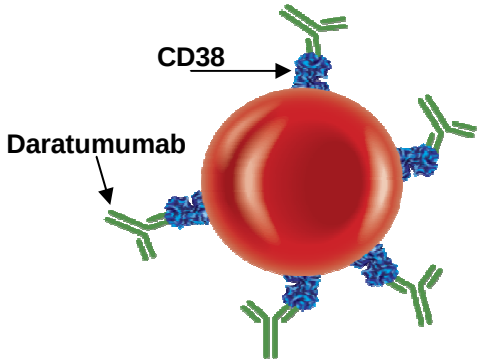
CAMELLIA overview

- RBCs express high levels of CD47
- Treatment with anti-CD47 is likely to cause anomalous grouping results
- If after treatment, the ABO group cannot be concluded, group O red cells may be required for transfusion
- In patients who have are DAT positive, adsorption studies can allow satisfactory antibody detection / identification in many cases.

Daratumumab overview

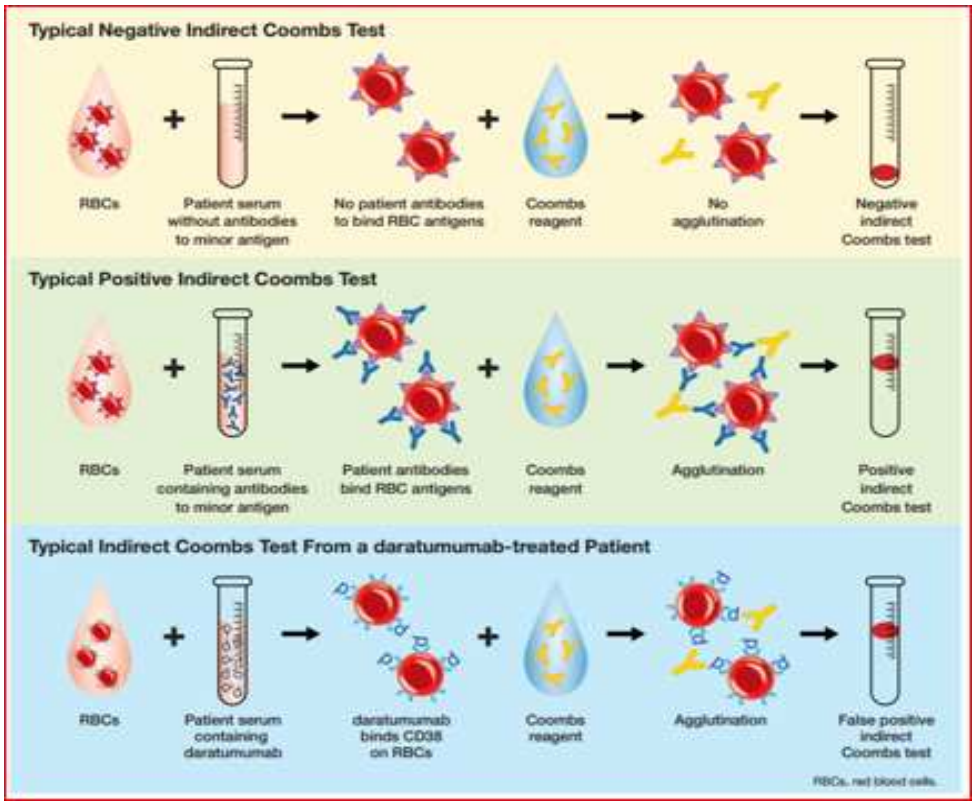
NHS Blood and Transplant

- Daratumumab is a human monoclonal antibody for the treatment of multiple myeloma.
- Daratumumab binds to CD38, a protein that is ubiquitously expressed on myeloma and lymphoma cells but expressed at low levels on normal lymphoid and myeloid cells.
- CD38 is also expressed at low levels on red blood cells (RBCs).
- To date, no clinically significant haemolysis has been observed in patients receiving 16 mg/kg Daratumumab.
- Among a cohort of 46 patients receiving Daratumumab at a dose of 16 mg/kg and requiring RBC and whole blood transfusions (135 transfusions received), no transfusion reactions have occurred.
- Recent approval of Daratumumab by NICE is expected to lead to an increase in the routine clinical use of Daratumumab.



Daratumumab binds to CD38 on RBCs

Daratumumab results in a false positive antibody screen



- Daratumumab is a human monoclonal antibody.
- Daratumumab binds to CD38, a protein expressed at low levels on red blood cells (RBCs).
- Daratumumab may mask the detection of antibodies in the patient's serum. This interferes with compatibility tests, including the antibody screening and crossmatching that are part of a routine pre-transfusion work up.

NHS
Blood and Transplant

Recommendations for serological testing - 1

- Prior to commencing monoclonal antibody therapy, it is recommended to undertake the following testing:
  - Baseline ABO and D group and antibody screen, and antibody identification if required
  - Direct antiglobulin test (DAT)
  - Undertake phenotype/genotype Rh CcDEe, MNSs, Kk, Jk^a, Jk^b, Fy^a and Fy^b groups.

NHS
Blood and Transplant

Recommendations for serological testing - 2

- Once Daratumumab (anti-CD38) therapy commenced
  - ABO and D type by normal methods
  - DAT may be positive (or negative)
  - The antibody screen / identification will be positive due to interference by the drug
  - The effect can persist for up to 6 months after treatment.

- Once CAMELLIA (anti-CD47) therapy commenced
  - ABO and D type as per normal method. If the ABO group cannot be concluded, group O red cells may be required for transfusion
  - In patients who have are DAT positive, adsorption studies can allow satisfactory antibody detection / identification in many cases.

Management of interference with blood compatibility testing by Daratumumab

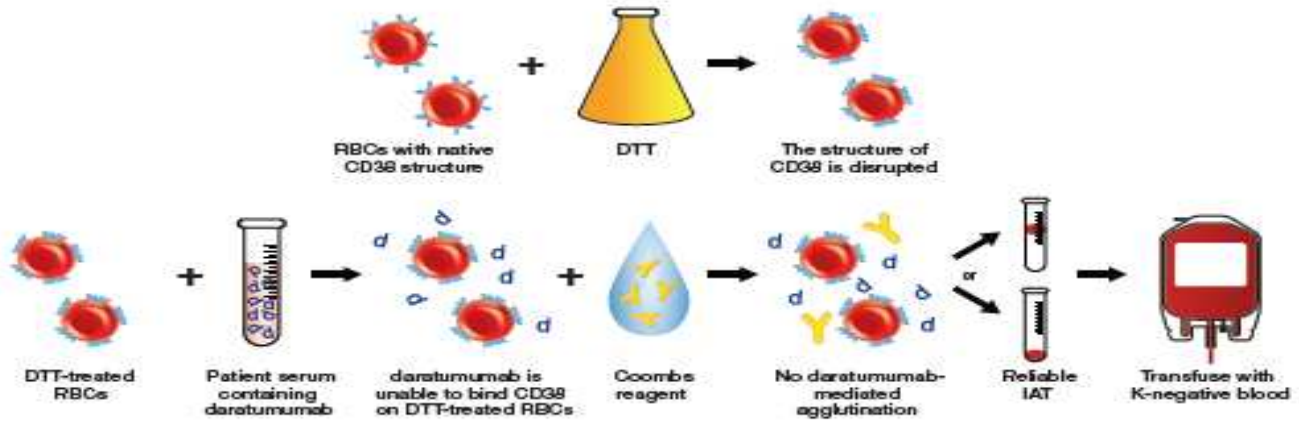
NHS Blood and Transplant

Treat reagent RBCs with DTT or locally validated methods

•Treat reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding, thus allowing antibody screening or cross-matching to be performed; (Chapuy *et al.* 2015*)* Alternative locally validated methods can also be used.

•Blood components for transfusion are identified for daratumumab-treated patients, after using DTT-treated reagent RBCs for antibody screening.

•Since the Kell blood group antigens are also sensitive to DTT treatment, units should be supplied which are matched for K- or k- patients, based on their phenotype or genotype, after ruling out or identifying alloantibodies using DTT-treated RBCs.



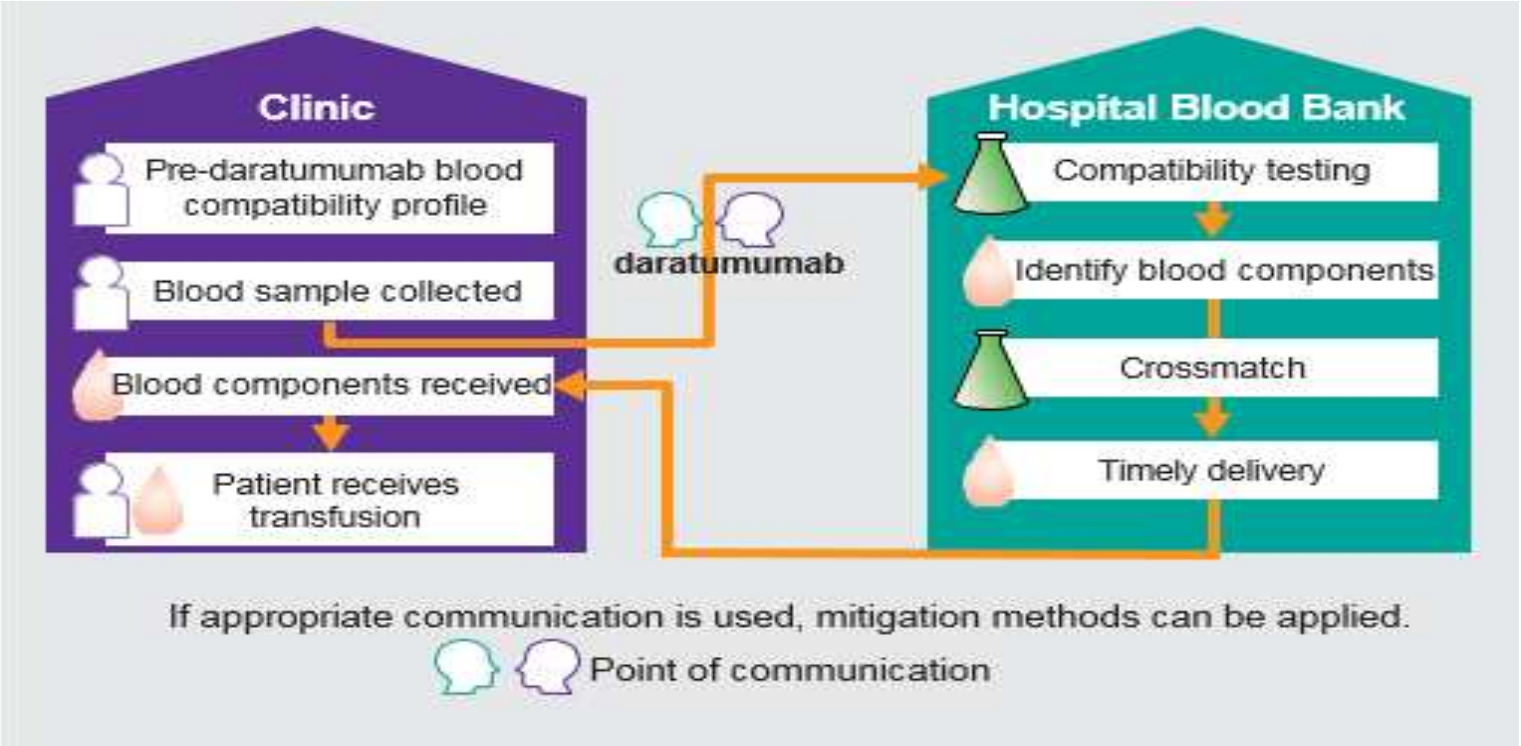
NHS
Blood and Transplant

Provision of blood

- Elective and non urgent transfusion - Provide ABO extended Rh and K compatible units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs.
- Irradiated blood components should be provided where required.
- If blood needed urgently can provide ABO extended Rh and K compatible pending further serological testing.
- In an absolute emergency - Uncrossmatched, ABO and D compatible RBC units should be administered as per local hospital transfusion laboratory practice.

NHS
Blood and Transplant

How to prevent blood transfusion delays – communication cascade



NHS
Blood and Transplant

Cascade the following key messages to hospital clinical teams

- To ensure that your patient receives a timely transfusion, send a group and screen sample prior to starting daratumumab and inform the blood bank that the patient is to commence daratumumab therapy.
- Inform shared care hospital
- Extended phenotyping/genotyping is recommended prior to starting daratumumab.
- If patients have already commenced daratumumab therapy it is essential to inform the blood bank.
- Specific techniques will be required for blood compatibility testing and blood component selection with likely referral to the NHSBT Red Cell Immunology (RCI) reference lab.
- This communication is essential to avoid delays in transfusion.

Inform the patient - provide a Patient Card

- Advise patients that they should carry their Patient ID Card for 6 months after the treatment has ended.
- Patient ID Card information includes
  - The name of the patient
  - If they are no longer taking daratumumab, the date they stopped treatment
  - Their blood type (A, B, AB, O, RhD+, RhD-) before starting daratumumab
  - Their antibody screen results before starting daratumumab.

Daratumumab PATIENTS: Provide this card to healthcare providers BEFORE blood transfusion and carry it for 6 months after treatment has ended. For further information, please refer to the Patient Information Leaflet

Patient ID Card for DARATUMUMAB

Name: _____

I am taking the following medication:

Daratumumab antibody product for the treatment of Multiple Myeloma

I stopped taking this medication on ____ / ____ / _____
DD MM YYYY

Before starting daratumumab my blood test results collected on

_____ / _____ / _____ were:
DD MM YYYY

Blood type: □ A □ B □ AB □ O □ RhD+ □ RhD-

Antibody screen was:

□ Negative □ Positive for the following antibodies:

_____

Other: _____

Contact details of institution where the blood tests were performed:

_____

NHS
Blood and Transplant

Action needed – effective communication

- Effective communication is essential between the following to ensure appropriate care and to avoid delays in transfusion:
  - Patients
  - Hospital consultants, trainees and nurses treating patients or covering on call
  - Hospital transfusion laboratories
  - Shared care hospitals
  - NHS Blood and Transplant Red Cell Immunohaematology (RCI) laboratories.
- Complete the contact details of the institution where the blood tests were performed on the patient card, it is especially useful in emergency situations.

NHS
Blood and Transplant

Further information

- The following information has been approved by the MHRA in accordance with their guidelines.
  - Healthcare Professional materials: https://www.medicines.org.uk/emc/RMM.539.pdf
  - Patient Card: https://www.medicines.org.uk/emc/RMM.540.pdf
  - Blood Bank: https://www.medicines.org.uk/emc/RMM.545.pdf

References

1. British Society for Haematology: Addendum to the Pre-Transfusion Compatibility Procedures in Blood Transfusion Laboratories, 2017 www.b-s-h.org.uk
2. Darzalex® UK Summary of Product Characteristics. 2017
3. Chapuy CI, et al. Transfusion. 2015;55(6 Pt 2):1545-1554
4. Albeniz I, et al. Hematology. 2007;12(5):409-414
5. Mehta K, et al. FASEB J. 1996;10(12):1408-1417
6. Zocchi E, et al. Biochem Biophys Res Commun. 1993;196(3):1459-1465
7. Westhoff CM, Reid ME. 2004;20(1):37-49
8. National Cancer Drugs Fund (CDF) List. (2018) Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1-68.pdf