Case Study: KK patient on Daratumumab

Dr Jennifer Laird
Consultant Haematologist
Daratumumab therapy in Myeloma

- Multiple Myeloma is an incurable plasma cell malignancy that accounts for 10% of all haematological cancers.

- Survival rates have improved steadily

  - Due to:
    - Improved diagnostic criteria
    - Better testing/sensitivity
    - Better supportive care
    - Better treatment options
      - New novel agents

Malignant plasma cells in bone marrow
Daratumumab: Mechanism of action

- IgG1 monoclonal antibody that binds CD38-expressing cells
  - CD38 is highly and ubiquitously expressed on myeloma cells\textsuperscript{a,b}
- Induces tumor cell death through direct and indirect mechanisms\textsuperscript{c-e}

DARATUMUMAB INTERFERENCE

**Typical Indirect Antiglobulin Test From a daratumumab-treated Patient**

- RBCs + Patient serum containing daratumumab → daratumumab binds CD38 on RBCs + Coombs reagent → Agglutination → daratumumab-mediated positive IAT
DARATUMUMAB INTERFERENCE MITIGATION METHODS

(1) Pre-treatment of screening red cell panels to remove CD-38 from membrane and prevent dara-induced panreactivity.
   (1) DTT (Dithiothreitol)
   (2) Trypsin
   (3) Papain
(2) Neutralisation of the CD38 monoclonal abs by antibodies or FAB fragments.
(3) Cord blood cells (low expression of CD38)
(4) Extended phenotype/genotype matched (without antibody exclusion)
DTT - Dithiothreitol

**Preparation**
- Powdered substance in 1 gm vials
  (1ml of PBS to reconstitute)
- Further diluted to 0.2M by mixing with further 31mls of PBS
- Ten drops of 0.2M DTT added to labelled vials and frozen (-18°C or below)
- Vials thawed at room temp

**H&S**
- Toxic – Avoid contact with skin/eyes; avoid inhalation
- Vials thawed at room temp
<table>
<thead>
<tr>
<th>DTT</th>
<th>Trypsin</th>
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<td>Cartwright (Yt&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Duffy</td>
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<tr>
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<tr>
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<td>Ch/Rg</td>
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<tr>
<td>Lutheran</td>
<td>Bp&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Xg&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
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<td>Ch/Rg</td>
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</table>
Gel Card Appearance

Before DTT

After DTT
If patient NAD after screening with DTT treated cells:

- Irregular antibody screen reported as POS then
  ‘No antibodies detected by IAT’
- Reporting comment “Antibody screen negative after treatment with DTT” added.

If an allo-antibody is detected post DTT treatment, sample is treated like a reference crossmatch and a BMS 2/3 must report
Case Presentation

Referral to Glasgow BTS reference centre from Inverness

Female Patient

Age: 76 years

Diagnosis: Relapsed Myeloma, To commence daratumumab. No recent transfusions

Tests Requested: Extended red cell phenotyping.
Clinical Information

- No recent transfusion
- 3 previous pregnancies
- No previous red cell antibodies
- 3rd relapse of myeloma, becoming symptomatic, to commence therapy with Daratumumab.
SNBTS DARATUMUMAB COMPATIBILITY PROCEDURE

- Pre-treatment sample is received for ABO/RhK/Full Group/ baseline Antibody screen/ID
- Patient file in Traceline updated with Protocol:
  - Important to be flagged ‘For Manual Testing Only’
    - due to ↑ risk of carry-over contamination

- Subsequent samples – Patient on DARA
  - ABO - no affected, should be able to be concluded
  - Ab Screen – 1/2+ strength pan-reactivity
  - Samples tested manually with DTT
Screening panel

3 Cell Screen Product Profile

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<tr>
<th>Product</th>
<th>Lot No</th>
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<td>CellStab</td>
<td>R122 3533</td>
<td>CellMedia</td>
<td>R123 3533</td>
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Unless otherwise indicated, all cells are positive for Kp\(b\) and Lu\(b\) and negative for Mr\(a\), Lu\(a\) and Co\(b\).

Instructions for use can be found at www.blood.co.uk/reagents

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<th>Le(a)</th>
<th>Le(b)</th>
<th>Fy(a)</th>
<th>Fy(b)</th>
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Cross-Referenced in Primary Document: SOP883
# Worksheet

**FULL PHENOTYPING WORKSHEET**

Test Set Up By: ............................................ Read By: ............................................ Checked By: ............................................ Date: ............................................

<table>
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<th>Name</th>
<th>Number</th>
<th>C&lt;sup&gt;W&lt;/sup&gt;</th>
<th>K</th>
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<th>Fy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fy&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Jk&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>S</th>
<th>s</th>
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**CONTROLS**

- **HOM**
- **HET**
- **NEG**

**ANTI-SERA USED**

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<th>Specificity</th>
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Cellano negative phenotype

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<th>RBC reaction with Anti-K Anti-k</th>
<th>Phenotype</th>
<th>Genotype</th>
<th>Approx. frequency: white black UK US</th>
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<tr>
<td>+</td>
<td>K+k-</td>
<td>KK</td>
<td>0.2% rare</td>
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<tr>
<td>+</td>
<td>K+k+</td>
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<td>8.8% 2%</td>
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<tr>
<td>-</td>
<td>K-k+</td>
<td>kk</td>
<td>91% 98%</td>
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Options appraisal

1) Give KK blood prophylactically to prevent anti-cellano

2) Give Kk blood and use an antibody screen that would detect anti-cellano (a number of viable suggestions)

3) Decide she is unlikely to form anti-cellano because of underlying disease
Patient Management plan

• Decided that patient should be transfused KK units for elective transfusions. This will require Donor team identifying compatible patients.
• In urgent cases A Pos K pos units should be provided
• When this is not possible and in life threatening emergencies, flying squad O Neg units should be used as necessary.
Daratumumab Guidance

- **NICE decision** (NICE TA510) March 2018

- **Recommended Daratumumab monotherapy for treating relapsed and refractory multiple myeloma**
  - Daratumumab (*Darzalex®*) monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if:
    - they have daratumumab after 3 previous therapies, **and**
    - the conditions in the managed access agreement are followed.
Daratumumab Guidance
Scotland

October 2018

following a resubmission considered under the end of life and orphan process:

**Daratumumab (Darzalex®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

SMC restriction: for use as a fourth line treatment option

In a pooled analysis of patients in a phase I/II and a phase II study, with heavily pre-treated multiple myeloma, who received the licensed dosing schedule of daratumumab, there was an overall response rate of 31%.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of daratumumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.
Daratumumab Guidance

- **NICE ta573**
- Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (April 2019)
- NICE TA573
- Daratumumab (Darzalex®) plus bortezomib plus dexamethasone is recommended for use within the Cancer Drugs Fund as an option for treating relapsed multiple myeloma in people who have had one previous treatment. It is recommended only if the conditions in the managed access agreement for daratumumab plus bortezomib plus dexamethasone are followed.
- Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.
- [www.nice.org.uk/guidance/ta573](http://www.nice.org.uk/guidance/ta573)
What has SMC said?

SMC has accepted daratumumab for the treatment of adults with multiple myeloma as described above. This acceptance is restricted to using daratumumab in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received one prior therapy only.
### Referral patterns in Scotland

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<th>Month / 2019</th>
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Transfusion requirements in Myeloma

Blood Requirements per Line of Treatment

Annual Transfusion Rate in Myeloma Patients per Line of Treatment (01/03/18 – 01/03/19)

Daisy Johnston
References


• Daralex R UK Summary of Product Characteristics. 2017

• Chapuy Cl et al, Transfusion 2015;55(6 Pt 2), 1545-1554

• British Society fo Haematology:Addendum to the Pretransfusion Compatibility Procedures in Blood Transfusion. 2017. [www.b-s-h.org.uk](http://www.b-s-h.org.uk)

• Therapeutic monoclonal antibodies & blood transfusion. NHSBT publication
Questions and discussion