Daratumumab and anti-CD38 therapy: a new front in myeloma therapy and an emerging complication in blood bank testing

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A clinical perspective and our experience at the Hospital of the University of Pennsylvania

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March 17, 2016

Multiple myeloma

- Neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin (antibody)
- Proliferate in bone marrow
- Common clinical presentations
  - Bone pain with lytic lesions discovered on routine skeletal films
  - Increased total serum protein concentration (monoclonal protein in the urine or serum)
  - Unexplained anemia
  - Hypercalcemia, sometimes symptomatic, sometimes incidental

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Fellow, Transfusion Medicine and Therapeutic Pathology
Department of Pathology and Laboratory Medicine

March 17, 2016
Diagnosis of Multiple Myeloma (traditional)

- Presence of an M-protein in serum and/or urine (no specific cutoff)
- Presence of 10 percent or more clonal bone marrow plasma cells
- Presence of related organ or tissue impairment
  - Calcium level
  - Renal insufficiency
  - Anemia
  - Bone lesions

The reality is much more complicated...

Treatment of Multiple Myeloma

- “Novel agents”
  - Immunomodulatory agents (IMiDs)
    - Thalidomide
    - Lenalidomide
    - Pomalidomide
  - Proteasome inhibitors
    - Bortezomib
    - Carfilzomib
- Steroids
- Other cytotoxic agents
  - Cyclophosphamide
  - Melphalan
- Autologous hematopoietic stem cell transplant
- The next generation: antibodies, histone deacetylase inhibitors, adoptive cellular therapies, targeted small molecular inhibitors
CD38
- Cyclic ADP ribose hydrolase
- Ectoenzyme catalyzes synthesis and hydrolysis of cyclic ADP-ribose
- Regulation of intracellular Ca^{2+}
- Receptor mediated adhesion

- Expressed on B, T, NK, plasma cells and red blood cells, among many others
  - Expression on plasma cells is very high, and is frequently used as a flow cytometric marker

Daratumumab (Darzalex™)
- Human monoclonal IgG1kappa that targets CD38
- Significant activity as monotherapy in heavily treated patients with relapsed or refractory disease
  - Infusion reactions are common, administered slowly in first infusion
  - Approved November 2015
  - At Hospital of the University of Pennsylvania, >30 patients treated so far

- LABORATORY INTERFERENCE
  - SPEP, antibody screening, and flow cytometry
  - Important: these are common to all anti-CD38 therapies
Why does anti-CD38 interfere with antibody screening?

- Daratumumab (or other anti-CD38 therapy) in patient's serum will react with reagent red blood cells in indirect antibody (IAT) testing.

Results from Chapuy et al and Oostendorp et al.

- Daratumumab potently interferes with routine blood bank serologic tests by directly binding to CD38 on RBCs
  - Seen up to 6 months after last dose
  - Seen with multiple anti-CD38 mAbs (in vitro)
- DAT results were variable
  - Is a subpopulation of high-expressing RBCs cleared?
  - Unknown
  - Is there clinically detectable hemolysis?
  - Not so far
- There are several strategies to resolve this interference
  - Anti-idiotype antibodies to neutralize daratumumab
  - Soluble extracellular domain of CD38
  - DTT treatment of reagent RBCs
  - Deratase CD38, prevents daratumumab and other anti-CD38 binding

DTT sensitive blood groups

<table>
<thead>
<tr>
<th>Blood group system name</th>
<th>Transfusion reaction potential</th>
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<tbody>
<tr>
<td>Kell (CD235a)</td>
<td>Immediate to delayed, mild to severe</td>
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<tr>
<td>Knops (ER1)</td>
<td>No (limited data)</td>
</tr>
<tr>
<td>Landsteiner-Wener (ICAM6)</td>
<td>Delayed, none to mild</td>
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<tr>
<td>Lutheran</td>
<td>No to moderate</td>
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<tr>
<td>Raph (C0515)</td>
<td>No to moderate</td>
</tr>
<tr>
<td>Cartwright</td>
<td>Delayed (rare), mild</td>
</tr>
<tr>
<td>Dombrock (ART4)</td>
<td>Highly variable, immediate to delayed, mild to severe</td>
</tr>
<tr>
<td>Indian (CD44H)</td>
<td>Decreased cell survival with IN1</td>
</tr>
<tr>
<td>John Milton Hagen (CD108/SEMA7A)</td>
<td>Delayed (rare), decreased cell survival</td>
</tr>
</tbody>
</table>

Adapted from The Blood Group Antigen Facts Book. Reid, Lomas-Francis, Ollsen
Acknowledgements

- Helen Carpenter, BSMT(ASCP)SBB
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- All transfusion medicine faculty and staff at HUP
- Meghan Herwig, BSN, RN, OCN
- Brendan Weiss, MD
- Physicians and nurses at HUP

Managing Anti-CD38 Interference in Blood Bank Testing

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Southeastern Michigan Region
Detroit, Michigan

Key references: anti-CD38 interference

1) When blood transfusion medicine becomes complicated to interference by monoclonal therapy

2) Resolving the daratumumab interference with blood compatibility testing

3) Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma
Anti-CD38 interference in lab tests

- Serum protein electrophoresis and immunofixation tests
  - Recognition and quantification of M-protein
  - Determine M-protein isotype. Confirm complete response
- Flow cytometry
  - Quantify normal and malignant plasma cells
- Blood compatibility testing

DARA interference: Serological characteristics

- Most patients developed weakly positive indirect antiglobulin test.
- Reactive with all cells tested – reagent RBC and donor units
- Reactive in all testing methods
  - Strength may depend on method and DARA concentration
- Reactive in diluted plasma
- Not removed by adsorption
- NOT a drug-induced antibody. Passively acquired

DARA and BB test methods

- Uniform reactivity with all cells
  - Tube - PEG, LIS, no enhancement
  - Gel-column tests
  - Strength varies (1+ to 2-3+)
- Solid Phase/Capture-R® tests
  - Less consistently positive; more variation in strength
  - may see neg and ?? in manual and automated
- Solid Phase/SolidScreenII®
  - Panagglutination (Chapuy et al)
DARA: BB management strategies

- Daratumumab anti-idiotypic antibodies (mouse anti-DARA)
  - Possibly need specific anti-idiotypic preparation for each formulation of anti-CD38

DARA: BB management strategies

Soluble CD38 (sCD38)
  - CD38 neutralizes the anti-CD38
  - Not available to react with CD38 on reagent RBC
  - Generic solution to anti-CD38 interference

Dithiothreitol treatment (DTT)
  - 5 disulfide bonds in CD38
  - Sensitive to reducing agents
  - Treatment of RBC with DTT destroys structure of CD38
  - No longer capable of reacting with circulating anti-CD38

Adapted from:
Oostendorp M, et al. Transfusion 2015;55;1555-1562
Figure S2 in online supplement

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0034918
Testing post-DARA infusion

- Initial antibody screen
- Confirm DARA administration
- DTT treat reagent red cells
- Repeat antibody screen

Exclusion of antibodies to common RBC antigens except anti-K

Report: reactivity is consistent with serological interference from circulating anti-CD38

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<tr>
<th>Scm</th>
<th>Gel-IAT</th>
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<tr>
<td>I</td>
<td>2+</td>
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<table>
<thead>
<tr>
<th>Scm</th>
<th>DTT treated</th>
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<tr>
<td>I</td>
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DTT treatment of RBC

- DTT treated RBC - not commercially available in US
- Purchase powdered DTT: 1 gram/5 grams
- 0.2M DTT: Dissolve 1 gram DTT in 32 ml PBS, pH 8.0

To treat:
- 1 volume washed packed RBC to 4 volumes 0.2M DTT
- Incubate at 37°C for 30-45 minutes
- Wash four times. Discard if excessive hemolysis
- Resuspend to 2-5% for testing

QC: Test treated and untreated cell for an antigen expected to be destroyed (k: anti-k)

DTT treatment – new test in BB?

- Must meet good laboratory practices for implementing a new test
  - Written procedure/training
  - Confirm expected performance: antigens destroyed
  - No false positive reactions with inert samples
  - Antibodies are detectable using treated cells when antigen is not destroyed.

- Expiration of DTT-treated cells?
  - No published data. Anecdotal: OK for at least 1 week
  - Studies underway
Is W.A.R.M.™ or ZZAP a substitute?

- Not an acceptable substitute for DTT treatment
- Contains DTT and papain/ficin
  (W.A.R.M.™ contains papain)
- Ficin/papain-sensitive antigens also destroyed
- W.A.R.M.™ or ZZAP-treated antibody screen would not detect antibodies to Fy\textsubscript{a}, Fy\textsubscript{b}, M, N, S

Risks of DTT-treated RBC approach

- Antigens destroyed by DTT
  - KEL (K, k, Kp\textsuperscript{a}, Kp\textsuperscript{b}, Js\textsuperscript{a}, Js\textsuperscript{b}, other KEL system Ag)
  - DO (Do\textsuperscript{a}, Do\textsuperscript{b}, Hy, Jo\textsuperscript{a}, other DO system Ag)
  - YT (Yt\textsuperscript{a}, Yt\textsuperscript{b})
  - KN (Kn\textsuperscript{a}, Kn\textsuperscript{b}, other KN system Ag)
  - LU (variable-Lu, other LU system Ag)
  - IN (In\textsuperscript{a}, In\textsuperscript{b}, other IN system Ag)
  - LW (Lw\textsuperscript{a}, LW\textsuperscript{b})
  - Raph
- Antibodies to these antigens will not be detected
- Transfuse K\textsuperscript{-} RBC

Use of genotyping for RBC antigens

- Predicted phenotype for common RBC antigens
  - Produce alloAb: some recommend phenotype-similar
- Predicted phenotype for many high-prevalence antigens that are destroyed by DTT
  - Platform dependent
  - Immucor PreciseType\textsuperscript{®} HEA: k, Kp\textsuperscript{a}, Js\textsuperscript{a}, Lw\textsuperscript{a}, Do\textsuperscript{a}, Do\textsuperscript{b}, Hy, Jo\textsuperscript{a}
- Are patient’s RBC predicted to lack a high-prevalence Ag? Is there a poor response to transfusion? Has there been a transfusion reaction?
  - Have a starting point for investigation
Other management strategies

- Trypsin-treat reagent RBC
  - Will cleave CD38 – no reactivity
  - Most other DTT-sensitive antigens are unaffected
  - Knops system antigens destroyed

- Use cord red blood cells
  - Postulated to have negligible CD38: non-reactive with DARA plasma (LISS-tube)
  - Can perform antibody exclusions if phenotype known
  - Could exclude underlying antibodies to high prevalence antigens (KEL, DO, YT antigens developed; LU, KN weak)


Other management strategies

- Test Lu(a-b-) RBC
  - In(Lu) cells appear to have low CD38
  - Decreased KN system, et al
  - Could perform antibody exclusion or screen for other antibodies to antigens of high prevalence
  - Depletion of rare cells

Vellequette RW, et al. Transfusion 2015;55 S3:28A

DARA and DAT/eluate

In vitro: incubation of donor RBC with DARA-spiked plasma
- Oostendorp et al. / Chapuy et al.
  - Panagglutination in acid eluate
  - Gel; flow cytometry

In vivo: red cells from patients receiving DARA
- Oostendorp et al – DAT negative/Neg eluate
- Chapuy et al – panagglutination in one pt tested
**DARA and DAT/eluate**

- DAT/AC frequently negative
- SEM IRL: 15 samples from 10 patients (6 hospitals)
  - positive DAT in 3 samples
  - Acid eluate: all negative (tube)

Similar anecdotal reports from other facilities:
- most: negative DAT
- occasional: positive DAT
- rarely: panagglutination in eluate

---

**Pos DAT and transfusion**

Patient receiving DARA and RBC transfusions

- Development of positive IAT
  - DTT treatment of test red cells; negative Ab screen
  - Transfuse incompatible K-1 red cells
  - DAT becomes positive

OR
  - History of RBC transfusion pre-DARA
  - Positive DAT discovered

Is it DARA or alloantibody? Need to perform elution studies. Not assume DAT+ due to DARA

---

**“It's all about Communication”**

A Case History

- 57 yo male
- Respiratory failure, congestive heart failure
  - "lots of diagnoses"
- Hgb 6.9
- Referral hospital testing:
  - Capture-PP: all cells strongly reactive but "control failure"
  - IRL antibody screen LISS and PEG: Neat autologous in both media

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Additional testing

- Panel PEG-IAT: all cells reactive 1+

<table>
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<tr>
<th>Saline-IAT</th>
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<th>Saline-IAT 1:10</th>
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<td>1+</td>
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<tr>
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<td>AC</td>
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<tr>
<td>Ficin-treated</td>
<td>DTT-treated</td>
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<tr>
<td>ASI</td>
<td>1+</td>
<td>0+</td>
</tr>
<tr>
<td>ASII</td>
<td>1+</td>
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Antibody to antigen of high prevalence?

- Cells tested positive
  - Multiple cells lacking Kn system antigens
    - Y(a−)

Many hours later....

- A nonreactive cell! Lu(a−b−) >1 cell tested

Is MM in the list of diagnoses? On Darzalex™? YES!

Case 2: MS

- 58 yo man IgG lambda multiple myeloma, p/w hypercalcemia
  - 11/2 autoSCT 10/2013, multiple therapies, now UPCC 51414
  - On 7/9/15: IgG 7.2

- First specimen (6/29):
  - Antibody screen positive: 1+ in cell / 1+ in cell II (in solid phase with Capture)
  - PEG reactivity against panel cells in gel (all 2+), autologous control 2−
  - DAT negative
  - Test tube method: variable positivity, with some negative, interpreted as anti-S plus inconclusive reactivity

- New specimen (7/8):
  - Similar pattern of reactivity, interpreted as possible HTLA antibody (w/u includes treatment with reducing agent)
  - Crossmatched 10 units, all 10 incompatible
  - BB later learns that patient on daratumumab, rules out all except K
Pattern of reactivity is unpredictable (screens and panels ranged from 0 to 4+)
Reactivity may be mistaken for other antibodies without knowledge of daratumumab
Misidentification may limit available donors in future transfusions

Case 3: JB

- 68 yr old woman with IgG lambda multiple myeloma
- On 7/13/15, presents for daratumumab
  - Fatigue; Hgb is 7.7
  - Transfusion planned for 7/14/15 at outside hospital
- Antibody screen + at outside hospital
  - Specimen sent to reference lab for workup (daratumab therapy noted on requisition)
  - Two days later (Thurs), workup not complete
- 7/16/15: Patient complains of SOB, wants to know if she can be transfused before the weekend
  - Patient referred to HUP for antibody screening and transfusion
  - Screen positive
  - Similar workup performed, all except K ruled out, x-matches all incompatible
Smaller hospitals do not have the capability to perform the testing required to rule out clinically significant antibodies and will send out testing. This may greatly delay transfusion at outside hospitals.

Experience at HUP thus far

- 59 patients treated with daratumumab
  - 43 patients with antibody screening performed post-treatment
- 32 positive antibody screens
  - 11 with negative antibody screens
  - 6 with antibody screens negative throughout
  - 6 positive antibody screens then negative
  - 6 patients had HTLA antibodies identified
    - Strongest reactivity generally seen in gel, sometimes weaker in solid phase
    - No definitive trends
    - Positive DATs in a small minority of specimens
      - 13 auto-control positive
      - 4 positive DAT (all at IgG only)
      - 1 with positive eluate
    - Transfusions being performed regularly in setting of daratumumab
      - No significant transfusion reactions thus far

Current policy at HUP

- All patients starting daratumumab must have type and screen prior to therapy
- Type and screen must be recorded on day of first infusion
- All test requisitions are labeled "Daratumumab Patient"; 2 pink-top tubes are recommended
- Urgent issues/questions are directed to blood bank resident or resident on call
- Number distributed to all nursing staff
- Transfusions are performed slowly, with close monitoring
- Clinics are aware that testing can take >1 day; they are carefully anticipating transfusion needs to plan for testing day prior if possible
- Crossmatch incompatible units are frequently required
- Updated 3-way verify strategy
- Built new antibody into our LIS as "anti-CD38"
Practical DARA management in the IRL

- Obtain history with sample submission, if possible.
- Test antibody screen/panel: All weakly positive
  - Any tube method tested
    - AC/DAT: pos or neg
  - Test Ficin-treated and DTT-treated Antibody screen
    - Ficin positive/DTT negative
- Dilute plasma 1:10 – still positive
- Ask caregiver specifically about MM and DARA
  - If no, test Lu(a-b-) cell.
  - If Negative, ask again. Request confirmation with Dr.

Practical DARA management in IRL

- Current caregivers may not know about DARA infusion.
  - Performed at outside clinic or another facility
  - Treatment may be unfamiliar to staff where patient is receiving current care.
- Listed diagnoses may focus on acute problem. Not chronic conditions.
- Darzalex™ will not likely be in “medication list.”

Streamlined DARA management

- If DARA treatment is known at time of sample submission:
  - Antibody screen to confirm reactivity
  - DTT-treated antibody screen
  - If negative, indicate K-1 RBC needed for transfusion
Immunotherapy management

Today - DARA. Tomorrow - ???

Information is the Key!

- Diagnosis
- Therapy
- Educated patient

Mitigation strategies at time of release

Reimbursement

Molecular Immunohematology: HEA

Joel de Jesus
Sr. Director, Government Affairs & Payer Relations

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Medicare Administrative Contractors (MACs)

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* Coverage in the NoviCare Solutions* jurisdiction may be covered through an alternate Local Coverage Determination.

Reimbursement Policy

Key information needed to submit or code for HEA reimbursement:

- CPT code to state procedure
- Z-code or descriptor for test used
- ICD-10 code to show medical necessity

Medicare, and other payers, may cover pre-transfusion molecular testing using the PreciseType HEA assay for the following categories of patients:

- Long term, frequent transfusions anticipated to prevent the development of alloantibodies
- Autoantibodies or other serologic reactivity that impedes the exclusion of clinically significant alloantibodies
- Suspected antibody against an antigen for which typing sera is not available; and
- Laboratory discrepancies on serologic typing

General Coding Guidance

- CPT code to state procedure
- Z-code or descriptor for test used
- ICD-10 code to show medical necessity
Next Step: LCD Optimization

- Officially expand MolDX LCDs:
  - Additional language specific to possible interfering substances
  - Include at least 3 additional ICD-10 codes for medical need justification:
    - C90.00 Multiple myeloma not having achieved remission
    - C90.01 Multiple myeloma in remission
    - C90.02 Multiple myeloma in relapse
  - Ideally, this would be a collaborative with medical practitioners and manufacturers.

Contact info: jdejesus@immucor.com

Q&A

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Thank you!