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

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

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

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Department of Pathology and Laboratory Medicine

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
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...

Table 1. IMWG diagnostic criteria for MM and related plasma cell disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IgM MGUS</td>
<td>All 3 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Serum monoclonal protein (non-IgM type) &lt; 3 g/dL.</td>
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<tr>
<td></td>
<td>Clonal bone marrow plasma cells &lt; 10%</td>
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<tr>
<td></td>
<td>Absence of end-organ damage, such as CRAB, that can be attributed to the plasma cell proliferative disorder</td>
</tr>
<tr>
<td>SMM</td>
<td>Both criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Serum monoclonal protein (IgG or IgA) &gt; 3 g/dL or urinary monoclonal protein &gt; 500 mg per 24 h and/or clonal bone marrow plasma cells 10%-60%</td>
</tr>
<tr>
<td></td>
<td>Absence of myeloma defining events or amyloidosis</td>
</tr>
<tr>
<td>MM</td>
<td>Both criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Clonal bone marrow plasma cells &gt; 10% or biopsy-proven bony or extramedullary plasmacytoma</td>
</tr>
<tr>
<td></td>
<td>Any one or more of the following myeloma defining events:</td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:</td>
</tr>
<tr>
<td></td>
<td>Hypercalcinemia: serum calcium &gt; 0.26 mmol/L (1 mg/dL) higher than the upper limit of normal or</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency: creatinine clearance &lt; 40 mL/min or serum creatinine &gt; 177 μmol/L (2 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Anemia: hemoglobin value of &gt; 2 g/dL below the lower limit of normal, or a hemoglobin value &lt; 10 g/dL</td>
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<tr>
<td></td>
<td>Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT</td>
</tr>
<tr>
<td></td>
<td>Clonal bone marrow plasma cell &gt; 60%</td>
</tr>
<tr>
<td></td>
<td>Involved: uninvolved serum FLC ratio &gt; 100 (involved FLC level must be &gt; 100 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 focal lesions on MRI studies (at least 5 mm)</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>All 3 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Serum IgM monoclonal protein &lt; 3 g/dL</td>
</tr>
<tr>
<td></td>
<td>Bone marrow lymphoplasmacytic infiltration &lt; 10%</td>
</tr>
<tr>
<td></td>
<td>No evidence of anemia, constitutional symptoms, hypercalcemia, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.</td>
</tr>
<tr>
<td>Light-chain MGUS</td>
<td>All criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Abnormal FLC ratio (≤ 0.28 or ≥ 1.65)</td>
</tr>
<tr>
<td></td>
<td>Increased level of the appropriate involved light chain (increased kappa FLC in patients with ratio &gt; 1.65 and increased lambda FLC in patients with ratio &lt; 0.28)</td>
</tr>
<tr>
<td></td>
<td>No immunoglobulin heavy-chain expression on immunofixation</td>
</tr>
<tr>
<td></td>
<td>Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder</td>
</tr>
<tr>
<td></td>
<td>Clonal bone marrow plasma cells &lt; 10%</td>
</tr>
<tr>
<td>Solitary plasmacytoma</td>
<td>Urinary monoclonal protein &lt; 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>All 4 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells</td>
</tr>
<tr>
<td></td>
<td>Normal bone marrow with no evidence of clonal plasma cells</td>
</tr>
<tr>
<td></td>
<td>Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)</td>
</tr>
<tr>
<td></td>
<td>Absence of end-organ damage, such as CRAB, that can be attributed to a lympho-plasma cell proliferative disorder</td>
</tr>
<tr>
<td>Solitary plasmacytoma with minimal marrow involvement*</td>
<td>All 4 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells</td>
</tr>
<tr>
<td></td>
<td>Clonal bone marrow plasma cells &lt; 10%</td>
</tr>
<tr>
<td></td>
<td>Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)</td>
</tr>
<tr>
<td></td>
<td>Absence of end-organ damage, such as CRAB, that can be attributed to a lympho-plasma cell proliferative disorder</td>
</tr>
</tbody>
</table>

* A bone marrow can be deferred in patients with low-risk MGUS (IgG type, M protein < 15 g/L, normal FLC myeloma.
* Solitary plasmacytoma with 10% or more clonal plasma cells is considered as MM.
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

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Table 1. Response rates with selected induction regimens among newly diagnosed myeloma patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>≥PR</th>
<th>≥VGPR</th>
<th>CR/nCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTD</td>
<td>190</td>
<td>85</td>
<td>60</td>
<td>95</td>
</tr>
<tr>
<td>CTD</td>
<td>91</td>
<td>90</td>
<td>68</td>
<td>25</td>
</tr>
<tr>
<td>RVD</td>
<td>66</td>
<td>100</td>
<td>67</td>
<td>39</td>
</tr>
<tr>
<td>CRD</td>
<td>65</td>
<td>96</td>
<td>81</td>
<td>62</td>
</tr>
<tr>
<td>CyBorD</td>
<td>63</td>
<td>90</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>VD + dara</td>
<td>6</td>
<td>100</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>VMD + dara</td>
<td>6</td>
<td>100</td>
<td>17</td>
<td>NR</td>
</tr>
<tr>
<td>VTD + dara</td>
<td>6</td>
<td>100</td>
<td>17</td>
<td>NR</td>
</tr>
</tbody>
</table>

VTD indicates bortezomib, thalidomide, and dexamethasone; CTD, carfilzomib, thalidomide, and dexamethasone; RVD, lenalidomide, bortezomib, and dexamethasone; CRD, carfilzomib, lenalidomide, and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; VD, bortezomib and dexamethasone; dara, daratumumab; VMD, bortezomib, melphalan, and dexamethasone; PR, partial response; VGPR, very good partial response; CR, complete response; nCR, near complete response; and NR, not reported.
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

Fabio Malavasi et al. Physiol Rev 2008;88:841-886
Daratumumab (Darzalex™)

- Human monoclonal IgG1 kappa 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

• LABORTORY INTERFERENCE
  - SPEP, antibody screening, and flow cytometry
  - Important: these are common to all anti-CD38 therapies
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Regimen</th>
<th>Schedule</th>
<th>N</th>
<th>Prior treatment</th>
<th>Response</th>
<th>TTE</th>
<th>Key toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zonder et al</td>
<td>Phase 1</td>
<td>Blotuzumab</td>
<td>MTD not reached; highest dose-level: elotuzumab 20 mg/kg iv; administered once every 2 weeks for 8 weeks; patients without PD or relapse prior to week 8 had the option to receive a second course of elotuzumab.</td>
<td>34</td>
<td>Median: 4.5</td>
<td>≥PR: 0%</td>
<td>Not reported</td>
<td>IRR before institution of infusion prophylaxis: 52%</td>
</tr>
<tr>
<td>Lokhorst et al</td>
<td>Phase 1/2</td>
<td>Daratumumab</td>
<td>MTD not reached; highest dose-level: daratumumab 24 mg/kg iv; in part 2, daratumumab 8 or 16 mg/kg iv was administered once-weekly for 8 times (schedules D and E: 3-week wash out period after infusion 1), and then biweekly for 14-16 weeks, followed by monthly infusions until PD/unacceptable toxicity.</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median: 4; Range: 2-12; Thal-refractory: 29%; Len-refractory: 74%; Bort-refractory: 71%; Carf-refractory: 17%; Pom-refractory: 36%</td>
<td>42</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median: 1.6; Range: 2-12; Thal-refractory: 29%; Len-refractory: 74%; Bort-refractory: 71%; Carf-refractory: 17%; Pom-refractory: 36%</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median PFS: 5.6 months; IRR: 74%; mostly grade 1/2 (grade 3 in 2%)</td>
<td></td>
</tr>
<tr>
<td>Lonial et al</td>
<td>Phase 2</td>
<td>Daratumumab</td>
<td>Initially daratumumab 8 or 16 mg/kg; 16 mg/kg was established as the recommended dose for further study. Daratumumab 16 mg/kg iv was administered once weekly for 8 weeks; every 2 weeks for 16 weeks, followed by monthly infusions.</td>
<td>Daratumumab 16 mg/kg; Median: 4; Range: 2-14; Thal-refractory: 44%; Len-refractory: 88%; Bort-refractory: 90%; Carf-refractory: 48%; Pom-refractory: 63%</td>
<td>198</td>
<td>Daratumumab 16 mg/kg; Median: 1.6; Range: 2-12; Thal-refractory: 29%; Len-refractory: 74%; Bort-refractory: 71%; Carf-refractory: 17%; Pom-refractory: 36%</td>
<td>Daratumumab 16 mg/kg; Median PFS: 4.7 months; IRR: 43%; mostly grade 1/2 (grade 3 in 2%)</td>
<td></td>
</tr>
<tr>
<td>Martin et al</td>
<td>Phase 1</td>
<td>Isatuximab</td>
<td>MTD not reached; highest dose-level: isatuximab 20 mg/kg iv; isatuximab was administered every 2 weeks or weekly.</td>
<td>Total patients with CD38+ hemoglobin: 39 MM patients: 35</td>
<td>MM patients: 35</td>
<td>≥PR: 39%</td>
<td>Not reported</td>
<td>MM patients treated with isatuximab ≥10 mg/kg; IRR: 43% (mostly grade 1/2)</td>
</tr>
<tr>
<td>Raab et al</td>
<td>Phase 1/2a</td>
<td>MOR202</td>
<td>MTD not reached; highest dose-level: MOR202 16 mg/kg iv; MOR202 was administered every 2 weeks or weekly.</td>
<td>MOR202 16 mg/kg; Median: 4; Range: not reported; Thal-refractory: 36%; Len-refractory: 98%; Bort-refractory: 100%; Carf-refractory: 7%; Pom-refractory: 16%</td>
<td>45</td>
<td>≥PR: 29%</td>
<td>Not reported</td>
<td>IRR: 40% in patients without dexamethasone as premedication, mostly grade 1/2 (grade 3 in 3%); IRR: 10% in patients with dexamethasone as premedication</td>
</tr>
<tr>
<td>Study</td>
<td>Type of study</td>
<td>Regimen</td>
<td>Schedule</td>
<td>N</td>
<td>Prior treatment</td>
<td>Response</td>
<td>TTE</td>
<td>Key toxicities</td>
</tr>
<tr>
<td>-------</td>
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<td>--------------------------------------------------------------------------</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Plesner et al&lt;sup&gt;44,45&lt;/sup&gt; (GEN503)</td>
<td>Phase 1/2</td>
<td>Daratumumab plus len-dex</td>
<td>MTD not reached; highest dose-level: Daratumumab 16 mg/kg iv weekly during the first 2 cycles, every other week during cycles 3-6, and monthly in cycle 7 and beyond until PD or unacceptable toxicity&lt;br&gt;Len: 25 mg by mouth on days 1-21 of 28-day cycle&lt;br&gt;Dex: 40 mg weekly</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median: 2&lt;br&gt;Range: 1-3&lt;br&gt;Thal: not reported&lt;br&gt;Len (not refractory): 34%&lt;br&gt;Bort: not reported</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median: 2&lt;br&gt;Range: 1-3&lt;br&gt;Thal: not reported&lt;br&gt;Len (not refractory): 34%&lt;br&gt;Bort: not reported</td>
<td>Not reported</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median: 2&lt;br&gt;Range: 1-3&lt;br&gt;Thal: not reported&lt;br&gt;Len (not refractory): 34%&lt;br&gt;Bort: not reported</td>
<td>Phase 2 with daratumumab 16 mg/kg; Median: 2&lt;br&gt;Range: 1-3&lt;br&gt;Thal: not reported&lt;br&gt;Len (not refractory): 34%&lt;br&gt;Bort: not reported</td>
</tr>
<tr>
<td>Chari et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Phase 1b</td>
<td>Daratumumab plus pom-dex</td>
<td>Daratumumab 16 mg/kg iv weekly during the first 2 cycles, every other week during cycles 3-6, and monthly in cycle 7 and beyond until PD or unacceptable toxicity&lt;br&gt;Len: 4 mg by mouth on days 1-21 of 28-day cycle&lt;br&gt;Dex: 40 mg weekly (20 mg for patients &gt;75 years of age)</td>
<td>77</td>
<td>Median: 3.5&lt;br&gt;Range: 2-10&lt;br&gt;Thal-refractory: not reported&lt;br&gt;Lenvatinib-refractory: 88%&lt;br&gt;Bort-refractory: 85%&lt;br&gt;Carfilzomib-refractory: 30%&lt;br&gt;Pi and IMid-refractory: 65%</td>
<td>53 patients with &gt; 1 post-baseline assessment; ≥ PR: 59%&lt;br&gt;VGPR: 23%&lt;br&gt;CR: 8%&lt;br&gt;Double-refractory patients (n=40); ≥ PR: 58%&lt;br&gt;Not reported</td>
<td>Not reported</td>
<td>IRR: 61%; little additional toxicity when daratumumab was added to pom-dex</td>
</tr>
<tr>
<td>Martin et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Phase 1b</td>
<td>Isatuximab plus len-dex</td>
<td>MTD not reached; highest dose-level: Isatuximab 10 mg/kg iv on days 1 and 15 of each 28-day cycle&lt;br&gt;Len: 25 mg by mouth on days 1-21 of 28-day cycle&lt;br&gt;Dex: 40 mg weekly</td>
<td>Isatuximab 10 mg/kg; Median: 4&lt;br&gt;Ranges: 1-9&lt;br&gt;Thal-refractory: NA&lt;br&gt;Lenvatinib-refractory: ~60%&lt;br&gt;Bort-refractory: ~63%&lt;br&gt;Carfilzomib-refractory: ~50%&lt;br&gt;Pi and IMid-refractory: ~30%</td>
<td>Isatuximab 10 mg/kg; Median: 4&lt;br&gt;Ranges: 1-9&lt;br&gt;Thal-refractory: NA&lt;br&gt;Lenvatinib-refractory: ~60%&lt;br&gt;Bort-refractory: ~63%&lt;br&gt;Carfilzomib-refractory: ~50%&lt;br&gt;Pi and IMid-refractory: ~30%</td>
<td>Whole group: 31</td>
<td>Whole group: Median PFS: 6.2 months&lt;br&gt;Whole group: IRR: 39% (grade 3 in 6%)</td>
<td>Whole group: Median PFS: 6.2 months&lt;br&gt;Whole group: IRR: 39% (grade 3 in 6%)</td>
</tr>
</tbody>
</table>

**Table 2. Selected studies with elotuzumab and CD38-targeting antibodies in combination with other agents in relapsed/refractory MM.**

*VAN DE DONK et al* | *BLOOD, 11 FEBRUARY 2016 • VOLUME 127, NUMBER 6* | *Penn Medicine*
Table 3. Selected ongoing studies with elotuzumab- and CD38-targeting antibody-containing regimens in newly diagnosed MM

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Setting</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01335399</td>
<td>3</td>
<td>Nontransplant eligible</td>
<td>Lenalidomide-dexamethasone vs lenalidomide-dexamethasone with elotuzumab</td>
</tr>
<tr>
<td>(ELOQUENT-1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02420860</td>
<td>2</td>
<td>Transplant eligible</td>
<td>Elotuzumab with lenalidomide as maintenance after auto-SCT</td>
</tr>
<tr>
<td>NCT02495922</td>
<td>3</td>
<td>Transplant eligible</td>
<td>Four study arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A1: RVD induction-auto-SCT–RVD consolidation–lenalidomide and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dexamethasone maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A2: RVD induction-auto-SCT–RVD with elotuzumab consolidation–lenalidomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and dexamethasone with elotuzumab maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B1: RVD with elotuzumab induction–auto-SCT–RVD consolidation–lenalidomide</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>and dexamethasone maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>lenalidomide and dexamethasone with elotuzumab maintenance</td>
</tr>
<tr>
<td>NCT02375555</td>
<td>2a</td>
<td>Transplant eligible</td>
<td>Elotuzumab plus bortezomib, lenalidomide and dexamethasone (patients have</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>option to undergo auto-SCT)</td>
</tr>
<tr>
<td>NCT01666719</td>
<td>1/2</td>
<td>High-risk MM and</td>
<td>Phase 1: Elotuzumab plus bortezomib, lenalidomide, and dexamethasone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>age ≥18 years</td>
<td>Phase 2: bortezomib-lenalidomide-dexamethasone vs bortezomib-lenalidomide-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dexamethasemide with elotuzumab</td>
</tr>
<tr>
<td>NCT01996971</td>
<td>1b</td>
<td>Irrespective of</td>
<td>Daratumumab combined with VD, VTD, or VMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>transplant eligibility for VD and VTD, and transplant ineligible for</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VMP</td>
</tr>
<tr>
<td>NCT02252172</td>
<td>3</td>
<td>Nontransplant eligible</td>
<td>Lenalidomide-dexamethasone vs lenalidomide-dexamethasone plus daratumumab</td>
</tr>
<tr>
<td>(Maia)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT02195479</td>
<td>3</td>
<td>Nontransplant eligible</td>
<td>VMP vs VMP with daratumumab</td>
</tr>
<tr>
<td>(Aloyne)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02541383</td>
<td>3</td>
<td>Transplant eligible</td>
<td>Randomization 1: VTD induction therapy–high-dose melphalan plus</td>
</tr>
<tr>
<td>(Cassiopeia; IFM 2015-01; HOVON 131)</td>
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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(er)-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**
    • Denatures CD38, prevents daratumumab (and other anti-CD38) binding
### DTT sensitive blood groups

<table>
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<th>Blood group system name</th>
<th>Transfusion reaction potential</th>
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<tr>
<td>Kell (CD238)</td>
<td>Immediate to delayed, mild to severe</td>
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<td>Knops (CR1)</td>
<td>No (limited data)</td>
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<tr>
<td>Landsteiner-Wiener (ICAM4)</td>
<td>Delayed, none to mild</td>
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<td>Lutheran</td>
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<td>Raph (CD151)</td>
<td>No to moderate</td>
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<td>Cartwright</td>
<td>Delayed (rare); mild</td>
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<td><strong>Highly variable, immediate to delayed, mild to severe</strong></td>
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<td>Indian (CD44)</td>
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<tr>
<td>John Milton Hagen (CD108/SEMA7A)</td>
<td>Delayed (rare), decreased cell survival</td>
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</table>

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

• Helen Carpenter, BSMT(ASCP)SBB
• Raeann Thomas, MT(ASCP)
• Rachel Davis-Rauser, BB(ASCP)
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• Vijay Bhoj, MD PhD
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• Meghan Herwig, BSN, RN, OCN
• Brendan Weiss, MD
• Physicians and nurses at HUP
Managing Anti-CD38 Interference in Blood Bank Testing

Janis R. Hamilton, MS, MT(ASCP)SBB
Manager, Immunohematology Reference Laboratory
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)

Potentially 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

Adapted from Oostendorp M, et al. Transfusion 2015;55;1555-1562
DARA: BB management strategies

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

Figure courtesy of:
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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<th>Gel-IAT</th>
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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 \textit{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^a, Fy^b, M, N, S
Risks of DTT-treated RBC approach

- Antigens destroyed by DTT
  - KEL ($K, k, Kp^a, Kp^b, Jsa, Js^b$, other KEL system Ag)
  - DO ($Do^a, Do^b, Hy, Jo^a$, other DO system Ag)
  - YT ($Yt^a, Yt^b$)
  - KN ($Kn^a, Kn^b$, other KN system Ag)
  - LU (variable-$Lu^b$, other LU system Ag)
  - IN ($In^a, In^b$, other IN system Ag)
  - LW ($Lw^a, LW^b$)
  - Raph
- Antibodies to these antigens will not be detected
- Transfuse K:-1 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®HEA: k, Kp^b, Js^b, Lu^b, Do^a, Do^b, Hy, Jo^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
  - \( \text{In}(LU) \) 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-R®: all cells strongly reactive but “control failure”

IRL antibody screen :LISS and PEG. Neg autocontrol in both media

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# Additional testing

- Panel PEG-IAT: all cells reactive 1+

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Antibody to antigen of high prevalence?

- Cells tested positive
  - Multiple cells lacking KN system antigens
  - Yt(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
  - s/p autoSCT 10/2013, multiple therapies, now UPCC 31414
  - On 7/9/15: Hgb 7.1

- First specimen (6/29):
  - Antibody screen positive: 1+ in cell I / 1+ in cell II (in solid phase with Capture)
  - Pan-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
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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 (dara 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 with positive antibody screens (most screens performed on Neo with solid phase/Capture methodology)
    • 11 with negative antibody screens
      • 6 with antibody screens negative throughout
      • 5 with antibody screens positive then negative
    • 6 patients had HTLA antibodies identified (all in cases without prior knowledge of anti-CD38 therapy)
  • Strongest reactivity generally seen in gel, sometimes weaker in solid phase
    • No definitive trends
• Positive DATs in a small minority of specimens
  • Of 30 specimens available for analysis
    • 13 auto-control positive
      • 4 positive DAT (all at IgG only)
        • 1 with positive eluate
      • 17 auto-control negative
  • No significant transfusion reactions thus far
Current policy at HUP

• All patients starting daratumumab must have type and screen prior to therapy
  • Nurses double-check record on day of first infusion
  • Currently using molecular testing for select cases

• All test requisitions are labeled “Daratumumab Patient”, 2 pink-top tubes are recommended
  • Using a specially colored sticker for rapid recognition on every specimen

• 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, so they are carefully anticipating transfusion needs to plan for testing day prior when possible

• Crossmatch incompatible units are frequently required
  • Outpatient myeloma clinics aware
  • Inpatient floors are contacted to explain the situation

• Built new antibody into our LIS as “anti-CD38”

• Meetings have been held with outpatient and inpatient nursing staff to promote education and communication
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
Disclaimers

- Contents of this presentation are specific to the PreciseType® HEA test which is an FDA approved (IVD) diagnostic test.
- The information contained in this presentation is provided to help you understand the reimbursement process, and is neither intended to tell you how to bill or code your claims, nor to suggest any manner in which you can increase or maximize reimbursement from any payer. All billing, coding, reimbursement, and appeals decisions must be made exclusively by the billing health services provider.
- The information in this presentation is for informational purposes only, and represents no promise, commitment, statement or guarantee by Immucor concerning proper billing or coding practices or levels of reimbursement, payment or charges. All Current Procedural Terminology (CPT®), Healthcare Common Procedural Coding System (HCPCS), Ambulatory Payment Classifications (APCs) or National Drug Classification (NDC) codes are provided for your information only and Immucor does not represent that these codes are or will be appropriate or that reimbursement will be made if using them or any other codes. CPT® codes and descriptions only are copyright by the American Medical Association. CPT®, APC and other codes do not include fee schedules, relative values or related listings. The Centers for Medicare & Medicaid Services (CMS) updates coding and coverage information frequently, and it is the responsibility of each health service provider to confirm the appropriate billing required by the local Medicare contractor.
- The information provided in this guide is based on publicly available Medicare reimbursement information gathered from the Center for Medicare and Medicaid Services (CMS) and is subject to change. For additional Medicare information, you should consult directly with your local Medicare Administrative Contractor. We recommend that you consult with your private payer organizations and state Medicaid programs with regard to their reimbursement policies. Immucor expressly disclaims any and all liability or responsibility for the billing, coding and claims submission of any third party that may choose to use this guide.
Medicare Administrative Contractors (MACs)

Palmetto GBA
June 22, 2015
CGS Administrators
October 5, 2015
Noridian
April 1, 2016
First Coast
July 21, 2015
National Govt Services
October 1, 2015
Novitas Solutions*
National Govt Services
October 1, 2015
Cahaba
April 1, 2016
WPS
October 1, 2015

* Coverage in the Novitas jurisdiction may be covered though an alternate Local Coverage Determination
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

**Assay Definition:**
Sickle-cell β-thal disease with acute chest syndrome

**About This Assay:**
METHODS: The BioAnalyze Imaging System (BioAnalyze) is used to capture the fluorescent signal from individual beads in an image to determine the genotype. The BioAnalyze software is configured as a BioChip, which includes the positive and negative control data. The BioAnalyze Imaging System (BASIS) software analyzes the BioChip data and correlates the reported genotype data to the patient's sample. The BioChip data includes the number of beads and the fluorescent signal data. The BioChip data is then analyzed by the BioAnalyze Imaging System (BASIS) software, which correlates the reported genotype data to the patient's sample.

**Intended Use:**
To aid in the diagnosis of sickle-cell β-thal disease with acute chest syndrome.

**Coding Guide for Immucor PreciseType HEA Molecular BeadChip Test**

**Category:**
Clinical Laboratory

**Code:**
- 8685
- 8686
- 8687
- 8688
- 8689
- 8690
- 8691
- 8692
- 8693
- 8694
- 8695
- 8696
- 8697
- 8698
- 8699

**Guidance:**
The most relevant genetic variants from each gene are shown in the table. The codes used for each gene are listed in Table 1. The codes for each gene are as follows:

- **Gene:**
  - **IC2-140:**
    - **Code:**
      - 8685
      - 8686
      - 8687
      - 8688
      - 8689
      - 8690
      - 8691
      - 8692
      - 8693
      - 8694
      - 8695
      - 8696
      - 8697
      - 8698
      - 8699

**Note:**
- **Code 8685:**
  - **Gene:**
    - **IC2-140:**
      - **Code:**
        - 8685
      - **IC2-140:**
        - **Code:**
          - 8686
      - **IC2-140:**
        - **Code:**
          - 8687
      - **IC2-140:**
        - **Code:**
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      - **IC2-140:**
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      - **IC2-140:**
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          - 8696
      - **IC2-140:**
        - **Code:**
          - 8697
      - **IC2-140:**
        - **Code:**
          - 8698
      - **IC2-140:**
        - **Code:**
          - 8699

**Additional Guidance:**
- The BioAnalyze Imaging System (BASIS) software is configured as a BioChip, which includes the positive and negative control data. The BioChip data is then analyzed by the BioAnalyze Imaging System (BASIS) software, which correlates the reported genotype data to the patient's sample.

**Coding Guide for Immucor PreciseType HEA Molecular BeadChip Test**

**Category:**
Clinical Laboratory

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**Note:**
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      - **IC2-140:**
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**Additional Guidance:**
- The BioAnalyze Imaging System (BASIS) software is configured as a BioChip, which includes the positive and negative control data. The BioChip data is then analyzed by the BioAnalyze Imaging System (BASIS) software, which correlates the reported genotype data to the patient's sample.
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
Continuing Education

• Each attendee must register for CE at:
  – https://www.surveymonkey.com/r/DARAweb

• Registration deadline is April 1, 2016

• Certificates will be sent via email only to those who have registered by April 15, 2016

• No registration for CE will be accepted after April 1, 2016

Thank you!