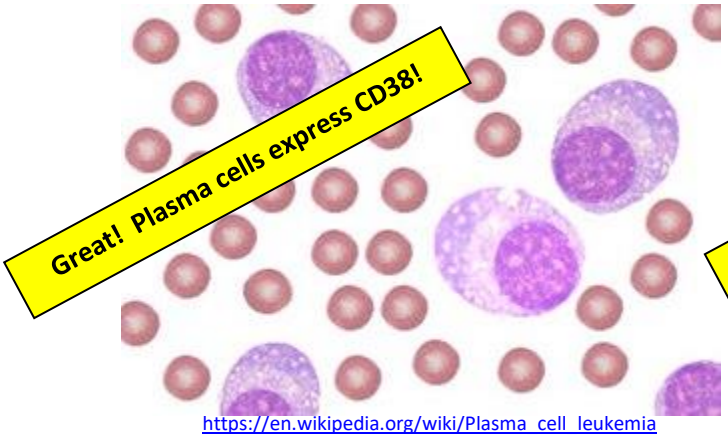
Anti-CD38 Monoclonal Antibody Therapy

Objectives:

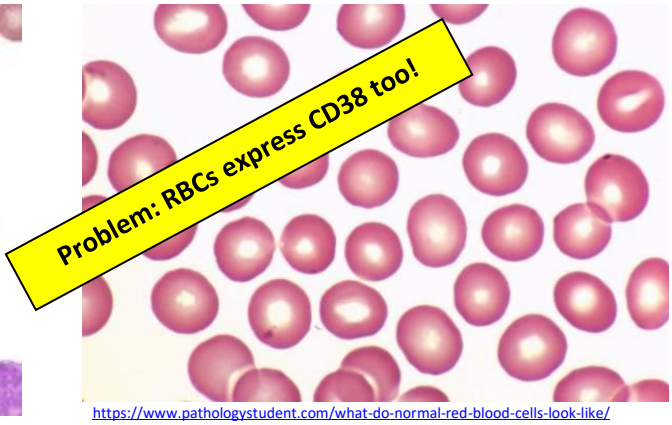
1. **Describe the interference of anti-CD38 monoclonal antibody in blood bank tests.**
2. **List ways to mitigate the serologic interference of anti-CD38.**
3. **Discuss transfusion strategies for patients receiving anti-CD38 therapy.**

Quick lesson:

In 2015, anti-CD38 monoclonal antibody (brand name _DARZALEX_, generic name _DARATUMUMAB_) was FDA-approved as a treatment for refractory multiple myeloma. Plasma cells prominent in the disease express CD38 strongly, so anti-CD38 is a targeted antibody that attacks the plasma cells of multiple myeloma.



https://en.wikipedia.org/wiki/Plasma_cell_leukemia



https://www.pathologystudent.com/what-do-normal-red-blood-cells-look-like/

Patients receiving anti-CD38 therapy have anti-CD38 in their plasma. Because RBCs express CD38 weakly, this interferes with pretransfusion testing. Anti-CD38 interferes with all tests by the indirect antiglobulin test (IAT).

This table describes the interference in the following tests:

Pre-transfusion testing	Interference observed with anti-CD38 therapy?
ABO	None
RhD	None
Antibody screen	All cells weakly reactive at IAT phase
Antibody panel	All cells weakly reactive at IAT phase
IAT crossmatches	All cells weakly reactive at IAT phase
DAT	Variable
Eluate (if applicable)	May be negative or may contain anti-CD38

***Warning: Anti-CD38 therapy is also used off-label for a variety of conditions**

Here's what anti-CD38 interference looks like in a serologic workup:

ABO/Rh					
Front type			Back type		**No anti-CD38 interference**
Anti-A	Anti-B	Anti-D	A_1 cells	B cells	
4+	0	4+	0	4+	

DAT		
Polyspecific AHG	Negative	**Anti-CD38 interference is variable.**

Antibody screen			
	RT	IAT	**Anti-CD38 interferes with IAT testing (all cells weakly positive)**
Screening cell I	0	1+	
Screening cell II	0	1+	
Screening cell III	0	1+	

Antibody panel																		
	Rh					Kell		Duffy		Kidd		MNS				Results		
	D	C	E	c	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	5' RT	IAT	
1	+	+	0	0	+	0	+	+	+	+	+	+	+	+	+	0	1+	**Anti-CD38 interferes with IAT testing (all cells weakly positive); Autocontrol results, like DAT, variable**
2	+	+	0	0	+	+	+	0	+	0	+	0	+	0	+	0	1+	
3	+	0	+	+	0	0	+	+	0	+	+	+	0	+	+	0	1+	
4	+	0	0	+	+	0	+	0	0	+	0	+	+	0	+	0	1+	
5	0	+	0	+	+	0	+	+	0	+	0	+	+	0	0	0	1+	
6	0	0	+	+	+	0	+	0	+	+	+	0	+	0	+	0	1+	
7	0	0	0	+	+	+	+	0	+	+	0	+	0	+	+	0	1+	
8	0	0	0	+	+	0	+	+	+	0	+	0	+	+	+	0	1+	
9	0	0	0	+	+	0	+	+	+	0	+	+	0	0	+	0	1+	
10	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	0	1+	
11	+	0	0	+	+	+	+	0	0	+	+	0	+	+	+	0	1+	
Auto																0	0	

Main problem with anti-CD38 interference:

If all cells are weakly reactive at IAT, then it is difficult to exclude the presence of alloantibodies.

Mitigating Anti-CD38 Interference: The most common way to mitigate anti-CD38 interference is by testing serologic CD38-negative cells. Most transfusion services or reference labs will use one or more of the following:

Serologic CD38-negative cells		
Cells	**Explanation**	**Downside**
DTT-treated reagent RBCs	Dithiothreitol, a reducing agent, destroys the CD38 molecule on reagent RBCs	DTT also destroys some blood group antigens (Kell, LU, YT, IN, DO). Unable to rule out corresponding antibodies.
Trypsin-treated reagent RBCs	The enzyme trypsin destroys the CD38 molecule on reagent RBCs	Trypsin also destroys some blood group antigens (LU, DO, IN, M & N antigens). Unable to rule out corresponding antibodies.
Cord cells	Cord cells are serologically CD38-negative	• Need to phenotype cord cells • Available in limited supply • Some antigens not fully expressed on cord cells
***InLu* cells**	The rare dominant serologic Lu(a-b-) cells are serologically CD38 negative	These are a rare resource only available in reference laboratories
DARA cells	Cells of patients who are receiving anti-CD38 therapy are serologically CD38-negative, as the therapy causes downregulation of the molecule on cells	• Need to phenotype DARA patient cells • Available in limited supply

Recommendations for transfusion of patients receiving anti-CD38 therapy:

- **Communication between heath care provider and transfusion service**
- **Obtain patient phenotype/genotype prior to beginning therapy**
    - **Why?**
        - **Know what antibodies a patient is at risk of making**
        - **May want to transfuse fully phenotype-matched units to avoid alloimmunization**

- **If testing DTT-treated cells is the only strategy used to rule out the presence of alloantibodies, give K- units**
    - **Why?**
        - **DTT destroys Kell antigens, and antibodies to Kell system antigens cannot be excluded using DTT-treated reagent cells**

- **Consider transfusing antigen-matched units**
    - **Why?**
        - **Prevent alloimmunization**
        - **Avoid costly complicated & repeated workups to rule out the presence of alloantibodies**

Case Study

Sample received in laboratory for a patient on anti-CD38 therapy for relapsed multiple myeloma. Initial results were as follows:

ABO/Rh					
Front type			Back type		**1. Interpretation:**
Anti-A	Anti-B	Anti-D	A_1 cells	B cells	
0	0	4+	4+	4+	

Antibody Panel																		
	Rh					Kell		Duffy		Kidd		MNS				Results		
	D	C	E	c	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	Untreated cells		DTT-treated cells
																5′ RT	IAT	IAT
1	+	+	0	0	+	0	+	+	+	+	+	+	+	+	+	0	1+	0
2	+	+	0	0	+	+	+	0	+	0	+	0	+	0	+	0	1+	0
3	+	0	+	+	0	0	+	+	0	+	+	+	0	+	+	0	1+	0
4	+	0	0	+	+	0	+	0	0	+	0	+	+	0	+	0	1+	0
5	0	+	0	+	+	0	+	+	0	+	0	+	+	0	0	0	1+	0
6	0	0	+	+	+	0	+	0	+	+	+	0	+	0	+	0	1+	0
7	0	0	0	+	+	+	+	0	+	+	0	+	0	+	+	0	1+	0
8	0	0	0	+	+	0	+	+	+	0	+	0	+	+	+	0	1+	0
9	0	0	0	+	+	0	+	+	+	0	+	+	0	0	+	0	1+	0
10	+	+	0	0	+	0	+	+	0	+	+	+	+	+	0	0	1+	0
11	+	0	+	+	0	+	+	0	0	+	+	0	+	+	0	0	1+	0
Auto																0	0	Not tested

Serologic phenotype											
	Anti-C	**Anti-E**	**Anti-c**	**Anti-e**	**Anti-K**	**Anti-Fy^a**	**Anti-Fy^b**	**Anti-Jk^a**	**Anti-Jk^b**	**Anti-S**	**Anti-s**
Patient cells	**+**	**0**	**0**	**+**	**0**	**+**	**+**	**0**	**+**	**0**	**+**

2. Which is the following is true regarding this serologic workup?

a. The patient's ABO/Rh typing was affected by anti-CD38
b. All alloantibodies to common red cell antigens were ruled out using DTT-treated cells
c. All alloantibodies to common red cell antigens were ruled out using untreated cells.
d. All alloantibodies to common red cell antigens were ruled out using DTT-treated cells, except antibodies to Kell system antigens.

3. Which of the following would be acceptable for transfusing this patient? (choose all correct answers)

a. Any group O+ unit
b. Any group O+ unit that is crossmatch compatible
c. Any group O+, K-negative unit
d. Group O+, fully phenotype-matched unit (E-, c-, K-, Jk(a-), S- units)

Case Study Answers

1. Group O, Rh positive
2. d
3. c, d

Assessing Understanding

1. **Which of the following is characteristic of anti-CD38 interference in pre-transfusion testing?**
    a. ABO discrepancies
    b. Invalid RhD results
    c. Extraneous reactivity detected at room temperature
    d. Extraneous reactivity detected by the indirect antiglobulin test (IAT)

2. **When using DTT-treated reagent RBCs to rule out alloantibodies to common red cell antigens for patients on anti-CD38 therapy, which of the following is recommended?**
    a. Transfuse K-negative donor units
    b. Transfuse units negative for Kell, DO, LU, YT & IN antigens
    c. Transfuse crossmatch-compatible units
    d. Do not transfuse

3. **How does anti-CD38 therapy affect a patient's direct antiglobulin test (DAT)?**
    a. Always positive because patient RBCs express CD38
    b. Always negative because multiple myeloma patient RBCs don't express CD38
    c. Variable: may be positive initially, then later negative due to downregulation of RBC CD38
    d. Unknown

Answers: 1. d; 2. a; 3. c