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Outcomes and Management of Red Blood Cell Transfusions in Multiple Myeloma Patients Treated With Daratumumab

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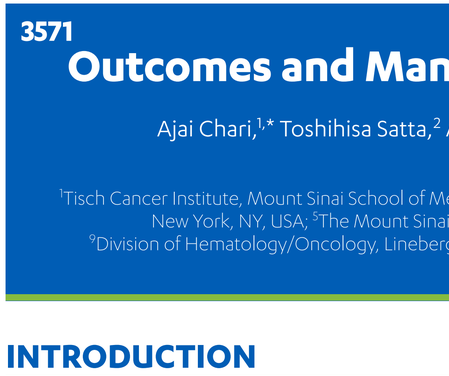
INTRODUCTION

- Daratumumab (DARA) is a first-in-class, human IgG1 monoclonal antibody in clinical development across the multiple myeloma (MM) spectrum
- DARA targets CD38, a protein that is highly expressed on MM cells[1,2]
- In 2 clinical studies of DARA monotherapy (16 mg/kg) in patients with relapsed and refractory MM (GEN501 [ClinicalTrials.gov Identifier: NCT00574288] and SIRIUS [NCT01985126]), overall response rates were 36% and 29%, respectively, including complete responses (CRs) and stringent CRs[3,4]
- Routine blood bank screening during the GEN501 study revealed unexpected false-positive indirect Coombs tests (also known as indirect antiglobulin tests; IATs) in DARA-treated patients. These tests are often performed to detect antibodies in recipient and donor blood before a red blood cell (RBC) transfusion[5,6]
- CD38 is expressed on human RBCs, and DARA may interfere with IATs by binding to endogenous CD38 on RBCs (**Figure 1**)



DARA, daratumumab; IAT, indirect antiglobulin test; RBC, red blood cell.

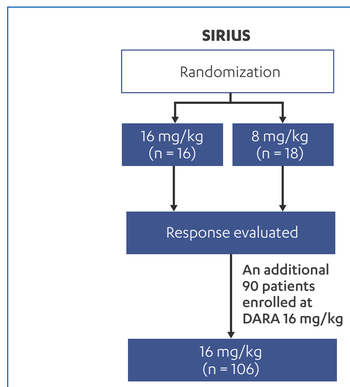
Figure 1. Mechanism of DARA interference in IATs.

- In the treatment setting of relapsed and refractory MM where patients are frequently anemic and often require RBC transfusions, DARA assay interference may cause a delay in the release of blood products from blood blanks
  - One strategy to negate DARA interference is to treat RBCs with dithiothreitol (DTT) to denature CD38 so that DARA binding is reversed[5]
  - Alternatively, RBC phenotyping may be initiated prior to the first DARA dose
- Presented here is an analysis of RBC transfusions and transfusion-related adverse events from the ongoing phase 2 SIRIUS study of DARA monotherapy in patients with relapsed or refractory MM, with a focus on the experience of 3 clinical sites

METHODS

Study Design

- Open-label, 2-part, international, multicenter, phase 2 study
- In Part 1, patients were randomized 1:1 to receive DARA 16 mg/kg weekly for 8 weeks, then every 2 weeks for 16 weeks, and every 4 weeks thereafter, or DARA 8 mg/kg every 4 weeks (**Figure 2**)
- Based on an interim analysis, the recommended dose (16 mg/kg) and dose schedule were established and selected for further study in Part 2



DARA, daratumumab.

Figure 2. SIRIUS study design.

Eligibility Criteria

- Documented MM and evidence of disease progression on or within 60 days of the most recent prior treatment regimen
- Evidence of response to ≥1 prior treatment regimen
- Received ≥3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), in any order during the course of treatment, or disease was double refractory to a PI and an IMiD
- Eastern Cooperative Oncology Group performance status of 0 to 2
- Patients who received prior allogeneic stem cell transplantation were excluded; patients could not have received autologous stem cell transplantation within 12 weeks before the first treatment cycle
- Excluded nonsecretory MM based upon standard *M*-component criteria, unless the baseline serum free light chain level was elevated

Blood Typing

- Patients were routinely RBC phenotyped by tube methodology prior to receiving their first dose of DARA
- If the patient's antibody screen was positive, antibody identification was performed using a panel of reagent RBCs
- Antibody screens were performed in gel cards using an automated ProVue® analyzer (ORTHO, Raritan, NJ)
  - RBC panels, including an autocontrol that tested a patients' RBCs against their own plasma, were performed using gel cards
- If panagglutination reactions on gel cards were detected, samples were manually tested further using low ionic strength saline (LISS)
  - LISS reduces the ability of DARA to bind to RBCs

Change in Hemoglobin Levels Post Transfusion

- The change in hemoglobin (Hb) per unit was calculated as the difference between the pre-transfusion value and a reading within 1 week of the transfusion date. If >1 post-transfusion value was recorded within 1 week, the mean of the differences per unit was reported

RESULTS

Transfusions in the Overall Study Population

- At a clinical cut-off date of January 9, 2015, 49 (40%) patients received 236 transfusions during treatment
  - 47 (38%) patients received a total of 147 transfusions of packed RBCs (PRBCs)
  - 17 (14%) patients received a total of 89 transfusions of platelets
- So far, only 1 transfusion-related reaction has been observed
  - The reaction occured following platelet, not RBC, transfusion

Transfusion Experience at Clinical Study Sites

- Experience with 10 patients is described, 8 from Mount Sinai and 1 each from the University of Salamanca and the University of North Carolina

Mount Sinai

Blood Typing

- Eight patients were enrolled at our institution and commenced treatment between March 4, 2014 and May 20, 2014
  - Antibody screening by IAT was performed on 7 patients prior to receiving their first DARA dose
  - Two patients showed multiple alloantibodies, including anti-E, anti-K, anti-Jkb, anti-Fya, anti-Fyb, anti-S, and anti-Knops (**Table 1**)
    - These patients and 5 others agglutinated all RBCs on panel testing, with weak reactivity at the antihuman globulin phase of testing
    - Six of these 7 patients had a negative autocontrol. One patient with a positive autocontrol had a weakly positive direct antiglobulin test with IgG
    - Six of these 7 patients with panagglutinin had a positive result on the first antibody screen and antibody identification panel by IAT after initiation of DARA, ranging from 7 to 175 days (median 49 days)
    - One patient did not have an IAT after initiation of DARA

Blood Transfusions

- A total of 9 leukoreduced, irradiated, phenotypically matched RBCs were given to 3 patients during DARA treatment (**Table 2**)
- An additional 9 units were given to 3 patients after DARA completion, while their IATs remained positive
- All transfusions resulted in an appropriate rise in Hb (median 1.0 g/dL, range 0.5-2.7)
- No associated transfusion reactions were observed
- None of the patients made new unexpected RBC alloantibodies while receiving phenotypically matched RBCs

University of Salamanca

- One patient was first treated in the study on April 9, 2014. No agglutination was present on blood panel testing (**Table 1**). The patient received 7 units of PRBCs after DARA treatment, with limited recovery of Hb levels (**Table 2**). No hemolysis was detected

University of North Carolina

- One patient was first treated in the study on April 21, 2014. Agglutination was present on blood panel testing (**Table 1**). Due to the panreactivity, the patient underwent RBC phenotyping prior to the transfusion and received 1 unit of PRBCs (**Table 2**)

Table 1. Blood Typing of Patients

Patient ID	RBC antigen antibody	Strength of panhemagglutinin	Additional comments
1	–	2+ (gel), 1+ (LISS)	AC negative, not enhanced by ficin
2	–	2+ (gel), 1+ (LISS)	AC 1+ (gel), AC– (LISS), DAT IgG 1+, eluate– (gel)
3	Anti-D and anti-E	1-2+ (gel), no reaction (LISS)	AC negative
4	–	1+ (gel), 0-1 (LISS)	AC negative
5	Anti-E, anti-K, anti-Jkb, anti-Fya, anti-Fyb, anti-S, and anti-Knops	2+ (gel), 1+ (LISS)	AC negative
6	N/A	N/A	N/A
7	–	2-3+ (gel), 1+ (LISS)	AC negative, negative at IS and 37
8	–	1+ (gel)	AC negative
9	–	Negative	Panagglutin not detected
10	Positive	1-2+ (gel), 1+ (LISS)	DAT IgG 1+ PEG W+ to 1+, PEG 37°–

RBC, red blood cell; AC, autocontrol; LISS, low ionic strength saline; DAT, direct antiglobulin test; N/A, not available.
Patients 1-8: Mount Sinai; Patient 9: University of Salamanca; Patient 10: University of North Carolina.

Table 2. Blood Transfusions

Patient ID	RBC units received on DARA treatment	RBC units received after DARA treatment	Hb difference per unit (g/dL)[a]
1	0	2	0.6, 0.5
2	4	0	0.8, 0.6, 0.6
3	0	1	2.2
4	1	0	1.8
5	4	0	0.3, 0.4
6	0	0	–
7	0	6	1.0, 1.3, 1.35
8	0	0	–
9	0	7	0.1, 0.2, 0.95, –0.9
10	1	0	0.7

RBC, red blood cell; DARA, daratumumab; Hb, hemoglobin.
[a]Patients may have received multiple units per transfusion.
Patients 1-8: Mount Sinai; Patient 9: University of Salamanca; Patient 10: University of North Carolina.

CONCLUSIONS

- **After DARA treatment, many patients who had an IAT demonstrated panreactivity on RBC panel testing**
- **Obtaining a RBC phenotype prior to initiating DARA treatment and providing phenotypically matched blood thereafter is one option that will avoid delays in providing compatible PRBCs[5]**
  - **Another option includes DTT denaturation of CD38 to reverse DARA binding to RBCs[5]**
- **These data align with observations from all 124 patients in the study, in that PRBC transfusions were not associated with complications**
- **In a patient population treated with DARA that will frequently require PRBC transfusion, blood bank and hematologist/oncologist awareness of these findings is important to minimize errors or transfusion delays**

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DISCLOSURES

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