A systematic review and meta- analysis of randomized controlled trials to evaluate the risk of hematological toxicities in patients with multiple myeloma treated with daratumumab

Myint A. Win¹, Kyaw Z. Thein², Ei M. Phyu³, Myat M. Han⁴, Nicholas D'Cunha², Lukman Tijani², Mark S. Currie¹, Donald Quick⁵, Kenneth Pendergrast¹

¹LewisGale Medical Center, VA; ²Texas Tech University Health Sciences Center, TX; ³Richmond University Medical Center, NY;

⁴The University of Texas MD Anderson Cancer Center, TX; ⁵Joe Arrington Cancer Research and Treatment Center , TX

INTRODUCTION

- Context:** Patients with multiple myeloma eventually develop a relapse despite the incorporation of proteasome inhibitors and immunomodulatory drugs. Addition of daratumumab (D) has resulted in high response rates with substantial survival benefits as well as considerable toxicities.

- Objective:** To determine the risk of hematological toxicities

METHODS

Literature search

- We performed a comprehensive literature search using MEDLINE, EMBASE databases, and meeting abstracts through April 30, 2018.
- The references of all potential studies were also reviewed for any additional relevant studies.
- All databases and meeting abstracts were systematically searched with the keywords 'Daratumumab' AND 'multiple myeloma'.
- We limited the search to 'humans' and 'randomized controlled trials'.
- All studies written in English or non-English languages were obtained.

Eligibility criteria

- The randomized controlled trials (RCTs) that were eligible to be included in the meta-analysis had to conform with the following characteristics:
 - Phase 3 RCTs comparing daratumumab based regimen and a control group in patients with multiple myeloma; and
 - Phase 3 RCTs that mention hematological toxicities as adverse effects.

Data extraction

- Three authors screened independently for eligibility and conducted data extraction from each eligible study. Disagreements were resolved by other two reviewers.

Study outcome measures

- The endpoints of our meta-analysis were hematological toxicities as adverse effects.

Data synthesis and analysis

- Mantel-Haenszel method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI).
- Heterogeneity was assessed using I^2 statistic.
- Random effects model was applied.
- P value less than 0.05 were considered significant.

RESULTS

- Patients or other participants:** Three phase 3 RCTs with a total of 1744 patients with multiple myeloma were eligible.
- Interventions:** The study arm used bortezomib (V), melphalan (M), prednisone (P) plus D; V, dexamethasone (Dex) plus D; and lenalidomide (R), Dex plus D. The control arm used V M P, V Dex, and R Dex. The randomization ratio was 1:1 in all studies. Daratumumab was utilized in relapsed and refractory multiple myeloma in the POLLUX study (n= 564) and the CASTOR study (n= 480) and as first-line treatment for patients with multiple myeloma who were ineligible for stem-cell transplantation in the ALCYONE study (n= 700). Figure 1 demonstrates the comprehensive steps of study selection. The characteristics of the studies were demonstrated completely in Table 1.

Fig. 1 Flow diagram of the study selection process

Table. 1 Characteristics of the studies included in the meta-analysis

Study	Author/ Year	Study Type	Sta dy Phs se	Line of Treatment	Number of Patients		Treatment
					Daratumumab	Control	
ALCYONE	Mateso/ 2018	Multicenter, Randomized, open-label, active-control	III	Untreated patients who are ineligible for stem cell transplantation	346	354	DVMP vs VMP
POLLUX	Dimopoulos / 2016	Randomized, open-label, multicenter	III	Relapsed or refractory	283	281	RDex vs RDX
CASTOR	Palumbo/ 2016	Multicenter, Randomized, open-label, active-control	III	Relapsed or refractory	243	237	DVDex vs VDX

RESULTS

Meta-analysis results

- The RR of all-grade side effects were as follows: anemia, 0.817 (95% CI: 0.711 – 0.939, p = 0.004); neutropenia, 1.285 (95% CI: 0.905 – 1.822; p = 0.160); lymphopenia, 1.962 (95% CI: 0.648 – 5.938; p = 0.233); and thrombocytopenia, 1.063 (95% CI: 0.818 – 1.382; p = 0.646).
- The RR of high-grade side effects were as follows: anemia, 0.769 (95% CI: 0.621 – 0.953, p = 0.016); neutropenia, 1.421 (95% CI: 0.972 – 2.077; p = 0.069); lymphopenia, 2.307 (95% CI: 0.933 – 5.702; p = 0.070); and thrombocytopenia, 1.071 (95% CI: 0.797 – 1.439; p = 0.649).

Pooled risk ratio for high-grade lymphopenia in patients with multiple myeloma receiving daratumumab containing regimen vs control arm

Pooled risk ratio for all-grade thrombocytopenia in patients with multiple myeloma receiving daratumumab containing regimen vs control arm

Pooled risk ratio for high-grade thrombocytopenia in patients with multiple myeloma receiving daratumumab containing regimen vs control arm

CONCLUSION

- Our study demonstrated that the risk of developing all grades of anemia was significantly reduced in daratumumab arm, favoring daratumumab.

REFERENCES

- Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *The New England journal of medicine*. 2016;375(8):754-766.
- Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet (London, England)*. 2016;387(10027):1551-1560.
- Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *The New England journal of medicine*. 2018;378(6):518-528.
- Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *The New England journal of medicine*. 2016;375(14):1319-1331.