Daratumumab-related pulmonary toxicities in patients with multiple myeloma: a systematic review and meta-analysis of phase III randomized controlled trials

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INTRODUCTION

- Context:** Daratumumab has shown to increase survival in patients with multiple myeloma through immune-mediated effects and immunomodulation by targeting CD38 which is highly expressed on myeloma cells.
- Objective:** To determine the risk of pulmonary toxicities in patients with multiple myeloma treated with daratumumab (D)

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 III RCTs comparing daratumumab based regimen and a control group in patients with multiple myeloma; and
 - Phase III RCTs that mention pulmonary toxicities as adverse effects.

Data extraction

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

Study outcome measures

- The endpoints of our meta-analysis were pulmonary 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:** A total of 1744 patients with multiple myeloma from 3 phase III RCTs were eligible.
- Interventions:** Studies compared D + bortezomib (V) + melphalan (M) + prednisone (P) vs VMP, D + lenalidomide (R) + dexamethasone (Dex) vs RDex and DVdex vs VDex. 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	Study Phase	Line of Treatment	Number of Patients		Treatment	
					Daratumumab	Control		
ALCYONE	Matesos/2018	Multicenter, Randomized, open-label, active-control	III	Untreated patients who are ineligible for stem cell transplantation	346	354	DVMP	VMP
POLLUX	Dimopoulos /2016	Randomized, open-label, multicenter	III	Relapsed or refractory	283	281	DRDex	RDex
CASTOR	Palumbo/2016	Multicenter, Randomized, open-label, active-control	III	Relapsed or refractory	243	237	DVDex	VDex

RESULTS

Meta-analysis results

- The RR of all-grade side effects were as follows: pneumonia, 1.495 (95% CI: 0.746 – 2.995, $p = 0.257$); upper respiratory tract infection (URTI), 1.597 (95% CI: 1.330 – 1.918; $p < 0.0001$); cough, 2.119 (95% CI: 1.621 – 2.772; $p < 0.0001$); dyspnea, 1.796 (95% CI: 1.314 – 2.455; $p < 0.0001$); and peripheral edema, 1.505 (95% CI: 0.856 – 2.644; $p = 0.155$).
- The RR of high-grade adverse effects were as follows: pneumonia, 1.313 (95% CI: 0.622 – 2.775, $p = 0.475$); URTI, 1.399 (95% CI: 0.621 – 3.149; $p = 0.418$); dyspnea, 4.428 (95% CI: 1.509 – 12.995; $p = 0.007$); and peripheral edema, 0.942 (95% CI: 0.199 – 4.464; $p = 0.940$).

CONCLUSION

- Patients on daratumumab experienced a significant increase in the risk of all grades of dyspnea with a relative risk of 4.42 for high grade dyspnea.
- Moreover, it is associated with all-grade URTI and all-grade cough.

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