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Research Article

Risk of Haematologic Side Effects in Multiple Myeloma Patients Treated with Daratumumab

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ABSTRACT

Background: Daratumumab is a novel monoclonal antibody (anti-CD38) drug that mainly for multiple myeloma patients. Hematologic adverse events are the most common in daratumumab-treated patients. However, the odds of daratumumab inducing the side effects have inadequate publications to support. This systematic review and meta-analysis were to investigate the hematologic safety of daratumumab.

Methods: PubMed, EMBASE, Scopus, Cochrane library, Google Scholar were used for searching eligible clinical trials systematically from January 2010 to August 2021, only randomized case control trials were included.

Results: Nine studies were included in the meta-analysis. The use of daratumumab associated with a lower risk of anemia (Odd Ratio [OR], 0.83; 95% Confidence Interval [CI], 0.72-0.96; I2=0%; P=0.01) but a significantly higher risk of thrombocytopenia (OR, 1.34; 95% CI, 1.02-1.76; I2=71%; P=0.04), neutropenia (OR, 1.83; 95% CI, 1.42-2.34; I2=70%; p<0.00001), and lymphopenia (OR, 1.53; 95% CI, 1.23-1.91; I2=21%; P=0.0002).

Conclusion: The administration of daratumumab increased the risk of thrombocytopenia, neutropenia, and lymphopenia in clinical trials, the risk of those events also increased. However, it showed a protective effect on anemia in clinical trials.

Keywords: Daratumumab; Multiple myeloma; Anemia; Thrombocytopenia; Neutropenia; Lymphopenia

INTRODUCTION

Multiple Myeloma (MM) is a type of cancerous growth of body cells that begins in the plasma cells of the bone marrow with unknown causes [1-3]. The drug treatments are often a combination therapy to maximize the anti-MM effect to achieve prolonged Progression-Free Survival (PFS). One such treatment is the combination of Bortezomib, Lenalidomide and Dexamethasone, which is one of the common types of first-line anti-MM therapy. The treatment for multiple myeloma that is commonly used is a combination of Immunomodulatory Drugs (IMiDs), Proteasome Inhibitors (PI), and corticosteroids. This first-line treatment widely used is the bortezomib-based regimen because it can be well tolerated in elderly patients and is associated with less thrombotic complications [4,5]. Although daratumumab can be used as a first line treatment, it is common that daratumumab is administered to Relapsed/Refractory Multiple Myeloma (RRMM) patients. However, almost all the MM patients will relapse over time regardless of the responses to the front-line treatment [6]. When the MM patient progresses to relapse, BOR can be substituted by another PI carfilzomib or anti-CD38 monoclonal antibody daratumumab added to the treatment regimen to target the CD38 antigen on the myeloma cells.

CD38 antigen is a 46-kDa type II transmembrane glycoprotein with multifunction such as cell adhesion, metabolisation, and signal transduction. It is also recognized as an ecto-enzyme, as it has the enzymatic function to catalyze the cyclisation of NAD to synthesis cADPR [7]. CD38 is universally expressed on different cells, including hematopoietic cells, osteoclasts and Purkinje cells. It is significantly expressed on multiple myeloma cells, therefore, anti-CD38 drugs are being introduced for the multiple myeloma patients as part of the immunotherapy.

Daratumumab is an antibody that targets the CD38 antigen on myeloma cells to produce an antibody-antigen complex that

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induces myeloma cells destruction in different mechanisms, including Complement-Dependent Cytotoxicity (CDC), Antibody-Dependent Cell-mediated Cytotoxicity (ADCC), Antibody-Dependent Cellular Phagocytosis (ADCP), and inducing apoptosis. Daratumumab is the most potent CDC inducer of all available anti-CD38 targets myeloma cells [8,9].

The use of daratumumab has several side effects. Infusion-related reactions are the most common with daratumumab; reactions include nausea, numbness, and swollen hands [10]. Hematologic side effects, including anemia, thrombocytopenia, and neutropenia, are often observed using the daratumumab-based regimen because CD38 is expressed on blood cells at different levels [11]. From the perspective of the pathology laboratory, daratumumab-treating patient's sample will interfere with the antibody screening Indirect Antibody Test (IAT) phase. As a result, pre-treatment antibody screening is recommended to minimize the risk of transfusion reaction in case of transfusion [12].

Since daratumumab is a comparably new drug first approved in 2015, the existing meta-analyses lacked adequate data to evaluate the hematologic adverse events in the patient compared to non-daratumumab-treating patients. Also, the hematologic side effects are crucial for the clinician as an indicator. For example, infection is one of the significant complications that could lead to death [13,14]. As a result, if the hematologic side effects are well understood, the prevention strategy can be implemented to avoid severe complications.

This systematic review and meta-analysis aimed to investigate the relation between daratumumab and the hematologic side effect to provide supportive data to the clinician on what is expected for the patient after administering daratumumab. The hypothesis is that daratumumab-treating patients have a greater chance of acquiring anemia, thrombocytopenia, neutropenia, and lymphocytopenia. All types of blood cells, including thrombocytes, erythrocytes, lymphocytes, and leukocytes, express diverse levels of CD38 on the surface. The addition of anti-CD38 therapy should target those antigens on normal blood cells and induce cell death as its mechanism on myeloma cells and lead to decreased blood cell counts.

METHODOLOGY

This meta-analysis is performed following the protocol from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15].

Search strategy

To obtain eligible electronic literatures for this meta-analysis, PubMed, EMBASE and Scopus were searched systematically from January 2010 to August 2021. The search terms "daratumumab" and "multiple myeloma" or "anemia" or "thrombocytopenia" were used on all electronic databases. Manual searches were performed using the same search terms above on Google Scholar, Cochrane Library, and ClinicalTrial.gov. In addition, study type "clinical trial" was added to identify eligible sources.

Study selection

Articles were retrieved by the search strategy and screened by using the designated exclusion and inclusion criteria to obtain the eligible articles for the meta-analysis. Suitable articles must be a study using the daratumumab-based regime or daratumumab monotherapy to treat multiple myeloma patients, the control group must be using the same backbone drugs but without daratumumab. Eligible studies must have at least one of the hematological adverse events recorded, including anemia, thrombocytopenia, neutropenia, and lymphocytopenia.

Exclusion criteria

The articles retrieved by the search strategy, were first screened based on the title to exclude any articles without a strong association with the meta-analysis purpose. Then, the abstract of the articles was reviewed and excluded any meta-analyses, literature reviews, and conference proceedings. Non-English or complete translation unavailable articles were excluded. Studies neither comparing with daratumumab nor unrelated to multiple myeloma patients were excluded. The remaining studies after title review were reviewed and assessed for eligibility. Any studies with a lack of control groups or no adverse event recorded were excluded. Any studies without full-text available on either RMIT library or public website were excluded. Case reports with less than two cases and repeated data were excluded at the final step.

Data extraction

Data were extracted from the eligible studies and grouped the relevant parameter with RevMan 5 for further investigation and comparison. The quality of all included studies was evaluated by using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist to guarantee the reliability of this meta-analysis [16].

Statistical analysis

The data was extracted from eligible articles as forest plots by using Review Manager (RevMan) software (Version 5.4. The Cochrane Collaboration, 2020.). Hematologic adverse events, including anemia, thrombocytopenia, neutropenia and lymphopenia, were expressed as Odd Ratios (OR) with 95% Confidence Intervals (CI). Random-effects model (DerSimonian and Laird method) was used to assess the overall effect of the meta-analysis; Mantel-Haenszel method was used to examine the heterogeneity with I2 statistics, below 40% indicated the heterogeneity of the meta-analysis was low, 30%-60% was moderate heterogeneity and above 50% is significant heterogeneity, Z-score and P-value were used to indicate its statistical significance, $P<0.05$ is considered statistically significant [17].

RESULTS

Study selection

Initially, 7,096 potential articles were obtained from PubMed, Scopus and Embase. An additional 37 potential articles were manually searched from Google Scholar, Cochrane Library, and ClinicalTrials.gov. 4,396 duplicate articles were excluded before the screening. 2,074 articles were excluded after the title screening of the article's relevancy to the meta-analysis, then, 552 articles were excluded by assessing its abstract. 111 papers were assessed for their eligibility, 101 were excluded, and nine eligible studies were obtained for meta-analysis after screening in Figure 1 [18-26].

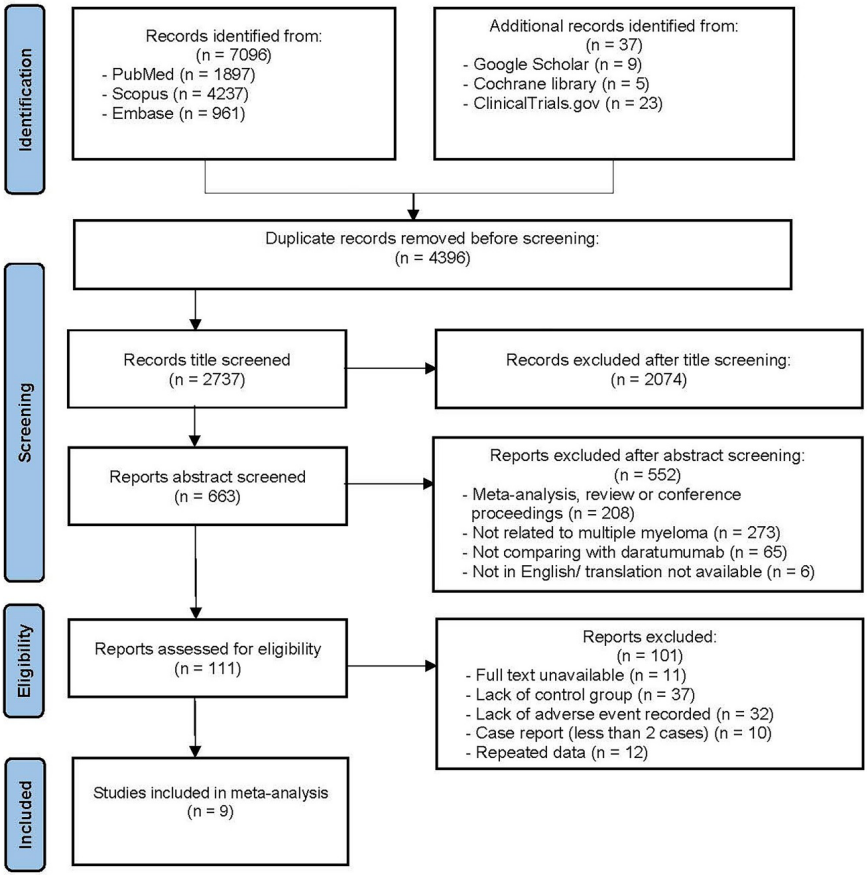

Figure 1: PRISMA flow chart for study identification, screening, eligibility, and inclusion for systematic review and meta-analysis on the risk of hematologic adverse events in the use of daratumumab.

Study characteristics

Selected studies were either phase two or phase three clinical trials conducted across multiple countries in 2014–2019, 5 studies were the research on Relapsed/Refractory Multiple Myeloma (RRMM) [18-20,22,25] and 4 studies were Newly Diagnosed Multiple Myeloma (NDMM) [21,23,24,26]. Median age of the studies was 58–71 with a median follow-up period of 7.4–28 months in Table 1.

At least three hematologic adverse events of interest were recorded in each included study with grading in Table 2 [18-30]. Non-daratumumab treating patients as control group was the selection criteria to show the comparison between two groups, any studies without a control group were excluded. Both groups in each study were using same regimen with or without daratumumab.

Table 1: Characteristics of the included studies.

Study	Study design	Regional countries	Study period	Disease indication	Median age (years)	Median follow up period (months)
Dimopoulos 2016 [18]	Phase 3 (POLLUX)	North America, Europe, nd the Asia Pacific Region	2014-2015	RRMM	65	13.5
Dimopoulos 2020 [19]	Phase 3 (CANDOR)	North America, Europe, nd the Asia Pacific	2017-2018	RRMM	64	17
imopoulos 2021 [20]	Phase 3 (APOLLO)	Europe	2017-2019	RRMM	67	16.9
Facon 2019 [19]	Phase 3 (MAIA)	North America, Europe, nd the Asia Pacific	2015-2017	NDMM	73	28
Lu 2021 [22]	Phase 3 (LEPUS)	Mainland China, Taiwan	2017-2019	NDMM	61	8.2
Mateos 2017 [23]	Phase 3 (ALCYONE)	North America, South America, Europe, the Asia Pacific	2015-2016	NDMM	71	16.5
Moreau 2019 [24]	Phase 3 (CASSIOPEIA)	Europe	2015-2017	NDMM	58	18.8
Palumbo 2016 [25]	Phase 3 (CASTOR)	Europe, North America, South America and the Asia Pacific	2014-2015	RRMM	71	7.4
Voorhees 2020 [26]	Phase 2 (GRIFFIN)	USA	2016-2018	NDMM	60	13.5

Note: RRMM: Relapsed/Refractory Multiple Myeloma; NDMM: Newly Diagnosed Multiple Myeloma.

Table 2: Haematologic adverse events reported in included studies.

A. All grades haematologic adverse events

Study	Regimen	Total patients (dara: non dara)	Haematologic adverse events (dara: non-dara patients)											
			Anaemia			Thrombocytopenia			Neutropenia			Lymphopenia		
			Dara	Non-dara	OR (95% CI)	Dara	Non-dara	OR (95% CI)	Dara	Non-dara	OR (95% CI)	Dara	Non-dara	OR (95% CI)
Dimopoulos 2016 [18]	DRd vs. Rd	(283 : 281)	88 (31%)	98 (35%)	0.84 (0.59- 1.20)	76 (27%)	77 (27%)	0.97 (0.67- 1.41)	168 (59%)	121 (43%)	1.93 (1.38- 2.70)	17 (6%)	15 (5%)	1.13 (0.55- 2.32)
Dimopoulos 2020 [19]	KdD vs. Kd	(308 : 153)	101 (33%)	48 (31%)	1.07 (0.7- 1.62)	115 (37%)	45 (29%)	1.43 (0.94- 2.17)	43 (14%)	15 (10%)	1.49 (0.80- 2.78)	27 (9%)	12 (8%)	1.13 (0.56- 2.30)
Dimopoulos 2021 [20]	DPd vs. Pd	(149 : 150)	55 (37%)	66 (44%)	0.74 (0.47- 1.18)	48 (32%)	50 (33%)	0.95 (0.59- 1.54)	105 (70%)	80 (53%)	2.09 (1.30- 3.36)	22 (15%)	12 (8%)	1.99 (0.95-4.19)
Facon 2019 [21]	DRd vs. Rd	(364 : 365)	126 (35%)	138 (38%)	0.87 (0.64- 1.18)	N/A	207 (57%)	154 (42%)	1.81 (1.35- 2.42)	66 (18%)	45 (12%)	1.57 (1.04-2.37)	60	60
Lu 2021 [22]	DVd vs. Vd	(140 : 68)	108 (77%)	53 (78%)	0.96 (0.48- 1.92)	127 (90%)	50 (74%)	3.52 (1.60- 7.71)	68 (48%)	17 (25%)	2.83 (1.49- 5.38)	80 (57%)	35 (51%)	1.26 (0.70-2.25)
Mateos 2017 [23]	D-VMP vs. VMP	(346 : 354)	97 (28%)	133 (38%)	0.65 (0.47- 0.89)	169 (49%)	190 (54%)	0.82 (0.61- 1.11)	172 (50%)	186 (53%)	0.89 (0.66- 1.20)	N/A	60	60
Moreau 2019 [24]	D-VTd vs. VTd	(536 : 538)	N/A	109 (20%)	73 (14%)	1.69 (1.18- 2.25)	157 (29%)	89 (17%)	2.09 (1.56- 2.80)	99 (18%)	67 (12%)	1.59 (1.14- 2.23)	60	60
Palumbo 2016 [25]	DVd vs. Vd	(243 : 237)	64 (26%)	74 (31%)	0.79 (0.53- 1.17)	143 (59%)	104 (44%)	1.83 (1.27- 2.63)	43 (18%)	22 (9%)	2.10 (1.21- 3.64)	32 (13%)	9 (4%)	3.84 (1.79- 8.24)
Voorhees 2020 [26]	D-RVd vs. RVd	(99 : 102)	35 (35%)	33 (32%)	1.14 (0.64- 2.05)	43 (43%)	36 (35%)	1.41 (0.80- 2.48)	57 (58%)	36 (35%)	2.49 (1.41- 4.40)	30 (30%)	28 (27%)	1.15 (0.62-2.12)

B. Grade 3-4 haematologic adverse events

Study	Regimen	Total patients (dara : non dara)	Grade 3-4 haematologic adverse events (dara : non-dara patients)											
			Anaemia			Thrombocytopenia			Neutropenia			Lymphopenia		
			Dara	Non-dara	OR (95% CI)	Dara	Non-dara	OR (95% CI)	Dara	Non-dara	OR (95% CI)	Dara	Non-dara	OR (95% CI)
Dimopoulos 2016 [18]	DRd vs. Rd	(283 : 281)	35 (12%)	55 (20%)	0.63 (0.43-0.93)	36 (13%)	38 (14%)	0.93 (0.57-1.52)	147 (52%)	104 (37%)	1.40 (1.16-1.70)	15 (5%)	10 (4%)	1.52 (0.67-3.44)
Dimopoulos 2020 [19]	KdD vs. Kd	(308 : 153)	51(17%)	22 (14%)	1.15 (0.73-1.83)	75 (24%)	25 (16%)	1.65 (1.00-2.72)	26 (8%)	9 (6%)	1.44 (0.69-2.99)	21 (7%)	11 (7%)	0.94 (0.44-2.01)
Dimopoulos 2021 [20]	DPd vs. Pd	(149 : 150)	25 (17%)	32 (21%)	0.79 (0.49-1.26)	26 (17%)	27 (18%)	0.96 (0.53-1.74)	101 (68%)	76 (51%)	1.34 (1.10-1.62)	18 (12%)	5 (3%)	3.98 (1.44-11.03)
Facon 2019 [21]	DRd vs. Rd	(364 : 365)	43 (12%)	72 (20%)	0.60 (0.42-0.85)	N/A	182 (50%)	129 (35%)	1.41 (1.19-1.68)	55 (15%)	39 (11%)	1.49 (0.96-2.31)	60	60
Lu 2021 [22]	DVd vs. Vd	(140 : 68)	35 (25%)	13 (19%)	1.31 (0.74-2.31)	72 (51%)	25 (37%)	1.82 (1.01-3.30)	23 (16%)	17 (25%)	0.66 (0.38-1.15)	61 (44%)	20 (29%)	1.85 (1.00-3.44)
Mateos 2017 [23]	D-VMP vs. VMP	(346 : 354)	55 (16%)	70 (20%)	0.80 (0.58-1.11)	119 (34%)	133 (38%)	0.87 (0.64-1.19)	138 (40%)	137 (39%)	1.03 (0.86-1.24)	N/A	60	60
Moreau 2019 [24]	D-VTd vs. VTd	(536 : 538)	N/A	59 (11%)	40 (7%)	1.54 (1.01-2.35)	148 (28%)	79 (15%)	1.88 (1.47-2.40)	99 (18%)	67 (12%)	1.59 (1.14-2.23)	60	60
Palumbo 2016 [25]	DVd vs. Vd	(243 : 237)	35 (14%)	38 (16%)	0.90 (0.59-1.37)	110 (45%)	78 (33%)	1.69 (1.16-2.44)	31 (13%)	10 (4%)	3.02 (1.52-6.03)	23 (9%)	6 (3%)	4.03 (1.61-10.07)
Voorhees 2020 [26]	D-RVd vs. RVd	(99 : 102)	9 (9%)	6 (6%)	1.55 (0.57-4.18)	16 (16%)	9 (9%)	1.99 (0.84-4.75)	41 (41%)	22 (22%)	1.92 (1.24-2.98)	23 (23%)	22 (22%)	1.10 (0.57-2.14)

Note: D- or D or dara: daratumumab; Rd: lenalidomide and dexamethasone; Kd: Carfilzomib and dexamethasone; Pd: pomalidomide and dexamethasone; Vd: bortezomib and dexamethasone; VMP: bortezomib, melphalan, and prednisone; VTd: bortezomib, thalidomide, and dexamethasone; RVd: lenalidomide, bortezomib, and dexamethasone.

Study quality assessment

Eligible studies were assessed for their quality following the STROBE guidelines to ensure the results were reliable in Table 3. All the studies had a clear abstract, introduction, method, result and discussion. However, only three studies explained how missing data were addressed [31,32-38], two of them explained how the loss to follow-up was addressed [31,32]. Three studies had not discussed the limitations of the study [33,34,37]. In general, the quality of the included studies was considerably high. They have a minimal risk of developing bias during the research process [30-38].

Meta-analysis on anemia

The meta-analysis on anemia was based on eight included studies [18-23,25,26], as one of the studies did not record the incidence of anemia [24], the results were summarized into a forest plot for interpretation. There is a notable difference between daratumumab-treated patients and non-daratumumab-treated patients (OR, 0.83; 95% CI, 0.72-0.96; I2=0%; P=0.01). In general, the results from all studies homogenously showed that the daratumumab might have a protective effect on anemia, two of the studies showed daratumumab have increased risk of anemia [19,26]. However, it was still statistically significant indicated that patients who administered daratumumab would have a 17% less chance to acquire anemia than the patients who did not in Figure 2A. The meta-analysis of the development of severe anemia was statistically insignificant (p>0.05).

Meta-analysis on thrombocytopenia

Since one study had no thrombocytopenia recorded, the meta-analysis on thrombocytopenia was based on 8 obtained studies [18-20,22-26]. There is a significant difference between two groups of patients (OR, 1.34; 95% CI, 1.02-1.76; I2=71%; P=0.04). The results were considerably highly heterogenous because 3 studies showed favors to daratumumab-treated patients [18,20,23] and 5 studies showed favors to non-daratumumab-treated patients with a particular study had an OR of 3.52 [19,22,24-26]. Though the high heterogeneity, the result is statistically significant showing that the use of daratumumab leads to a 34% higher risk of developing thrombocytopenia in Figure 2B. The chances of daratumumab-treated patients develop a severe thrombocytopenia was 31% higher than the control group (OR, 1.31; 95% CI, 1.03-1.68; I2=52%; P=0.03) in Figure 2C.

Meta-analysis on neutropenia

All selected studies were included for the meta-analysis on the incidence of neutropenia [18-26]. The results showed a highly significant difference between two groups of patients (OR, 1.83; 95% CI, 1.42-2.34; I2=70%; p<0.00001). The results showed highly heterogenous because one of the studies particularly reflected favor to daratumumab-treated patients with an OR of 0.89 [23], while the others were all favor to control group and the OR were close to 2. The result indicated that the administration of daratumumab had 83% higher risk of developing neutropenia than the patients did not administer daratumumab in Figure 3A. The chance of developed to severe neutropenia was 47% higher in the daratumumab group (OR, 1.47; 95% CI, 1.17-1.69; I2=73%; P=0.0002) in Figure 3B.

Meta-analysis on lymphopenia

There is one study excluded from the meta-analysis because it did record the development of lymphopenia during the follow-up period, 8 studies were included in the meta-analysis on the prevalence of lymphopenia [18-22, 24-26]. The result showed moderate difference between two groups (OR, 1.53; 95% CI, 1.23-1.91; I2=21%; P=0.0002). The forest plot showed a low heterogeneity with all data and indicated favor to the control group. The result showed that the use of daratumumab had 53% increased risk of lymphopenia than the patients treating with only the backbone drugs in Figure 3C. The opportunity of serious lymphopenia is 78% higher (OR, 1.78; 95% CI, 1.33-2.40; I2=46%; P=0.0001) in Figure 3D.

Table 3: Quality assessment of included studies following STROBE checklist.

Item	Reference								
	Dimopoulos, 2016 [18]	Dimopoulos, 2020 [19]	Dimopoulos, 2021 [20]	Facon, 2019 [21]	Lu, 2021 [22]	Mateos, 2017 [23]	Moreau, 2019 [24]	Palumbo, 2016 [25]	Voorhees, 2020 [26]
Eligibility criteria and the methods of selection of participants	Y	Y	Y	Y	Y	Y	Y	Y	Y
Address the potential sources of bias	Y	Y	Y	Y	Y	Y	Y	Y	Y
Explain how missing data were addressed	N	Y	Y	N	N	N	N	N	Y
Detailed method assessment	Y	Y	Y	Y	Y	Y	Y	Y	Y
Report numbers of individuals and give reasons for non-participation at each stage of the study	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discuss potential limitations	Y	Y	Y	N	N	Y	Y	N	Y

Note: Y: criteria fulfilled; N: criteria unfulfilled.

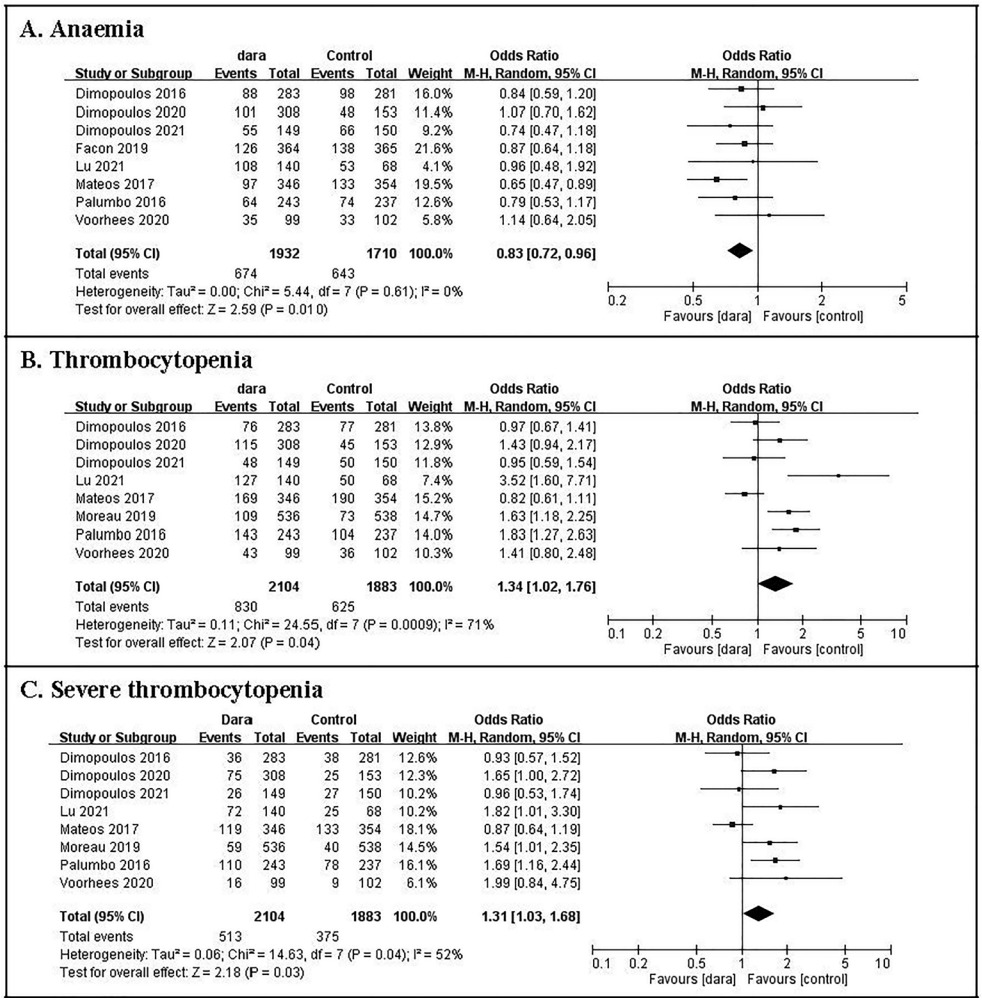

Figure 2: Incidence of hematologic adverse events: forest plot. (A) The incidence of anaemia, (B) thrombocytopenia, (C) severe thrombocytopenia were expressed as the Odd Ratio (OR) with 95% Confidence Intervals (CI), random-effect model (DerSimonian and Laird method) was used for the overall effect, and Mantel-Haenszel method (M-H) was used for the heterogeneity. Statistical significance of the forest plot was expressed as Z-score and P-value; heterogeneity was described as I2 with a different P-value. The weight was defined as % regarding the size of each study.

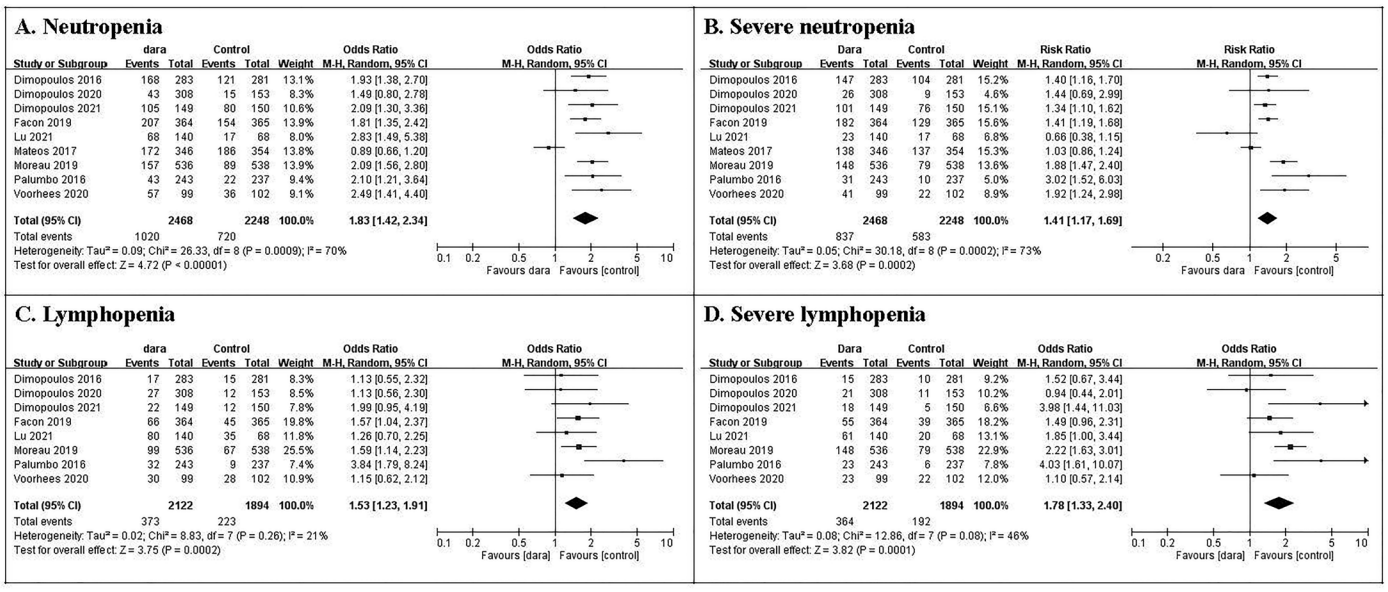

Figure 3: Incidence of hematologic adverse events: Forest plot. (A) The incidence of neutropenia, (B) severe neutropenia, (C) lymphopenia, (D) severe lymphopenia were expressed as the Odd Ratio (OR) with 95% Confidence Intervals (CI), random-effect model (DerSimonian and Laird method) was used for the overall effect, and Mantel-Haenszel method (M-H) was used for the heterogeneity. Statistical significance of the forest plot was expressed as Z-score and P-value, heterogeneity was described as I2 with a different P-value. The weight was defined as % regarding the size of each study.

DISCUSSION

In the past few years, daratumumab has significantly lengthened PFS in both Relapsed/Refractory Multiple Myeloma (RRMM) and Newly Diagnosed Multiple Myeloma (NDMM) patients [18-26]. However, it has a higher chance of developing adverse events in various degrees, and indirectly leading to death. In this meta-analysis, the risk of thrombocytopenia, neutropenia, and lymphopenia was higher in patients who received a daratumumab-based regimen than the patients who only used the backbone drugs, it matched the hypothesis as blood cells are known to express CD38 antigens on their surface. Interestingly, daratumumab has shown a protective effect on anemia. CD38 is recognized as one of the surface markers on erythrocytes, and this is explained by the interference of the pre-transfusion antibody screening IAT phase [27].

Eight clinical trials were incorporated to compare the prevalence of anemia in daratumumab and non-daratumumab treating patients. The meta-analysis result showed that the use of daratumumab has a lower risk of anemia (OR, 0.83; 95% CI, 0.72-0.96), which is against the hypothesis, as it is known that erythrocytes expressed CD38 antigen on the cell surface [28]. The data from the included studies revealed no statistical difference between the two groups in terms of severity. Nevertheless, the daratumumab is less likely to destroy the red cells by its mechanisms, the daratumumab-treated patient sample commonly has either a weak positive or a negative Direct Antibody Test (DAT) result that indicates the hemolytic reaction induced by the drugs is unlikely [29,30]. However, the IAT phase panagglutination result in the daratumumab-treated patient indicates that the monoclonal antibodies can attach to the red cells [31,32]. The IAT and DAT tests explained that the daratumumab-treated patients were free of hemolytic reaction induced by the drug.

Sullivan et al. conducted a study to investigate the CD38 expression on red cells following daratumumab treatment. It found that daratumumab could induce the loss of CD38 antigen on the red cells instead of killing them, this also prevents further daratumumab engagement and protect red cells from ongoing daratumumab-based treatment [33]. The phenomenon of antibodies inducing loss of red cell surface antigens, usually through the Fcγ receptor-dependent pathway, has been shown in murine model studies [34,35] and some case reports [36-38], however, the exact mechanism that causes the loss of surface antigens remains unknown.

The study has been done based on the CD38 expression of the blood cells, it has showed that the use of daratumumab decreased the CD38 expression level on the multiple myeloma cells and non-tumour immune cells. Monocytes and granulocytes took the CD38 antigens by trogocytosis on multiple myeloma cells and non-tumor immune cells, thus, the antibody-antigen complex is shifted to the monocytes and granulocytes [39].

Eight clinical trials were included to examine the possibility of thrombocytopenia in daratumumab and non-daratumumab treating patients. The result indicated that the use of daratumumab has an increased risk of thrombocytopenia (OR, 1.34; 95% CI, 1.02-1.76), which can be explained by the CD38 expression on thrombocytes [40]. Moreover, the result determined that the patients treated with daratumumab have a higher chance of developing severe thrombocytopenia (OR, 1.31; 95% CI, 1.03-1.68; I2=52%; P=0.03).

Platelets are known as a crucial component for hemostasis, they are responsible for ceasing bleeding. Severe platelet deficiency can lead to life-threatening complications, such as spontaneous bleeding. If the platelet deficient patient is bleeding internally, it is a medical emergency but hard to observe initially. Since a lack of platelet prolongs the bleeding time, the risk is significantly higher when the patient bleeds [4]. Therefore, the thrombocyte level should be monitored regularly to avoid severe thrombocytopenia. Platelet products can be considered for thrombocytopenia patients due to the daratumumab treatment to replenish their platelet concentration in the blood.

The result from the included studies suggested that the administration of daratumumab had a markedly increased chance of acquiring neutropenia (OR, 1.83; 95% CI, 1.42-2.34). It could be because of the nature of neutrophil (CD38 expression) or the internalization of the anti-CD38-antigen complex on erythrocytes or multiple myeloma cells [39]. The result also suggested the patient using daratumumab would have a higher chance of acquiring serious neutropenia (OR, 1.47; 95% CI, 1.17-1.69; I2=73%; P=0.0002).

Neutrophil has been known as the first-line defender in the human immune system. Severe neutropenia will lead to recurrent infection [41,42]; for multiple myeloma patients, it could result in death, as it is one of the common fatal factors for them [13,14]. As a result, the significant decrease of neutrophils must be addressed during the daratumumab treatment by a full blood exam to determine the neutrophil count.

The result reveals that the risk of lymphopenia is high in daratumumab-treated patients (OR, 1.53; 95% CI, 1.23-1.91). Compare to the non-daratumumab treated patients, the risk of severe lymphopenia is almost doubled (OR, 1.78; 95% CI, 1.33-2.40; I2=46%; P=0.0001). As mentioned, lymphocytes express a certain level of CD38 on the surface, which explains the decrease of lymphocytes after daratumumab administration [11].

Since the data shows the high risk of neutropenia and lymphopenia in this study, the prevention strategy must be considered before starting the treatment to minimize the risk of death because of infections, such as sepsis. Prophylactic Granulocyte Colony-Stimulating Factor (G-CSF) is suggested to stimulate the neutrophil progenitor cells proliferation, activation, and differentiation [43]. Alternatively, prophylactic antibiotics can be considered, they can limit infection risk by eliminating the bacteria as soon as possible. Both approaches suggest a similar effect in countering infectious complications [44].

One of the limitations of this meta-analysis is that the available data is inadequate; there is no daratumumab monotherapy clinical trial eligible for this meta-analysis. Daratumumab is a new drug being used in the last few years, the clinical trials mainly focused on its efficacy but not the hematologic adverse event. Besides, the mechanism of daratumumab reducing the CD38 antigens on the red cell surface still remains unknown, the protective effect on anemia is unclear. Although the use of daratumumab might not cause anemia, the patient can potentially develop anemia due to other reasons such as chronic blood loss and drug-induced anemia due to other medications. As a result, it is crucial to have the pre-transfusion blood grouping and antibody screening preceding the administration of daratumumab.

Further study on the CD38 reductions after daratumumab-based treatment will be supportive for the researcher to understand the potential resistance of daratumumab because the CD38 reduction is not only present on erythrocytes but also appears on the multiple

myeloma cells [39,45]. Furthermore, the serious infection is the primary cause of death in multiple myeloma patients, it will be helpful to research deceased post-daratumumab treatment patients to evaluate their cause of death. The raised incidences of neutropenia and lymphopenia will more likely lead to a serious infection in daratumumab-treated patients than those who did not use daratumumab as part of the treatment. As a result, though the daratumumab seems to be beneficial to the PFS, its side effects should not be overlooked as it could be more problematic than the growth of tumor.

CONCLUSION

The use of daratumumab has strong evidence that it is beneficial to PFS. However, the data have shown that the treatment has an increased risk of severe thrombocytopenia, neutropenia, and lymphopenia but present with a protective effect on anemia. Therefore, a pre-treatment prophylactic strategy should be considered before the start of the treatment. The mechanism of daratumumab protect from anemia is unclear, however, it is suggested that CD38 antigens on the erythrocytes were taken by monocytes and granulocytes by trogocytosis could be one of the reasons. In the future, more studies based on the mechanism and safety of daratumumab would allow health professionals to understand the resistance of the drug.

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DISCLOSURE

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