Efficacy and safety of plerixafor for hematopoietic stem cell mobilization for autologous transplantation in patients with non-Hodgkin lymphoma and multiple myeloma: A systematic review and meta-analysis

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Received May 10, 2019; Accepted June 17, 2019

DOI: 10.3892/etm.2019.7691

Abstract. Plerixafor in combination granulocyte-colony stimulating factor (G-CSF) has been used for the mobilization of hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). The aim of this study was to systematically search the published literature and analyze evidence on the efficacy of additional plerixafor for successful HSC mobilization in patients with NHL and MM, and to evaluate the safety of the drug. The PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Google scholar databases were searched electronically for studies published in the English language up to March, 2019. Five studies (3 on NHL and 2 on MM) were included in this review article. The meta-analysis of data of 364 patients in the treatment group and 368 patients in the control group, indicated that the mobilization of ≥5/6x10^6 $CD34^+$ cells/kg in 4 or less apheresis days was superior with plerixafor + G-CSF than with G-CSF alone (RR=2.59, 95% CI: 1.40 to 4.81; P<0.0001). Similarly, a greater proportion of patients in the treatment group exhibited the mobilization of ≥2x10^6 $CD34^+$ cells/kg in 4 or less apheresis days (RR=1.46, 95% CI: 1.01 to 2.12; P=0.04). The addition of plerixafor significantly increased the total collection of $CD34^+$ cells (random: MD=4.21; 95% CI: 2.85 to 5.57; P<0.00001). Meta-analysis indicated no significant increase in adverse events with the addition of plerixafor for HSC mobilization (RR=1.03, 95% CI: 0.99 to 1.06; P=0.16). On the whole, the findings of this study indicate that the addition of plerixafor to G-CSF leads to an increased HSC collection in a shorter period of time with no concomitant increase in adverse events. Further randomized controlled trials with a larger sample size evaluating short term efficacy, as well as long term survival would help to further strengthen the evidence on this subject.

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Key words: hematopoietic stem cell, plerixafor, lymphoma, multiple myeloma

Introduction

High-dose chemotherapy along with autologous hematopoietic stem cell transplantation (HSCT) is a widely used effective therapeutic option for patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). HSCT has greatly evolved from its early days where the only source for the harvesting of hematopoietic stem cells (HSCs) was the bone marrow. A paradigm shift in HSC collection has been made possible with the use of granulocyte-colony stimulating factor (G-CSF) to increase the number of circulating $CD34^+$ cells and improvements in collection devices, which allows for HSC collection in fewer apheresis sessions (1,2).

Successful HSCT is largely dependent on the adequate collection of $CD34^+$ cells. The American Society for Blood and Marrow Transplantation recommends 4-5x10^6 $CD34^+$ cells/kg as the optimal number and ≥2x10^6 $CD34^+$ cells/kg as the minimum number of HSCs to support transplantation (3). A large number of cases, however, are hard-to-mobilize or require multiple mobilization attempts for successful HSCT. The number of patients who are 'difficult mobilizers' varies considerably, with an incidence ranging from 5 to 10% to approximately 30% (2,4,5). In general, greater mobilization issues have been found in patients with NHL compared to those suffering from MM (5).

Plerixafor, a novel bicyclam small-molecule, was initially developed for managing HIV infections. It reversibly binds to chemokine receptor CXCR4 and antagonizes the chemokine stromal cell-derived factor-1α (SDF-1α) interaction, thereby inducing the mobilization of stem cells into the bloodstream from the bone marrow (6,7). It has been approved in the US and EU for the collection of HSCs and autologous transplantation in patients with NHL and MM, when used in combination with G-CSF (8). A number of literature reviews describing the role of plerixafor

in HSC mobilization have been published (2,9,10). However, to date, and at least to the best of our knowledge, level-1 evidence in the form of a systematic review and meta-analysis has been conducted only once (11). The published review analyses data from the first 2 randomized controlled trials (RCTs) were conducted by DiPersio *et al* in 2009 (12,13). With the addition of new studies (14,15) from different centers on the efficacy of plerixafor for HSCT, there is a need for an updated meta-analysis. Therefore, the aim of this study was to systematically search the published literature and analyze evidence on the efficacy of additional plerixafor for successful HSC mobilization in patients with NHL and MM, and to evaluate the safety of the drug.

Data and methods

This systematic review of the literature was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (16) and guidelines of the Cochrane Handbook for Systematic Reviews of Intervention (17).

Eligibility criteria. We included studies conducted on patients with NHL or MM, in first or second complete or partial remission, who were eligible for autologous HSCT and had not undergone any prior failed mobilization or HSCT. Study intervention was the use of additional plerixafor for HSC mobilization compared to placebo or no additional therapy. The outcome of the trial was to report the number of patients achieving optimal HSC mobilization, the time required to achieve optimal HSC mobilization and adverse events. Non-English language studies, studies on healthy volunteers, uncontrolled and non-randomized studies were excluded.

Search strategy. We searched the PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Google scholar databases (first 100 results) electronically for articles published up to March, 2019. The key words used in various combinations were as follows: Lymphoma [MeSH], multiple myeloma [MeSH], non-Hodgkin lymphoma [MeSH], plerixafor [MeSH], plerixafor hydrochloride [MeSH], granulocyte-colony stimulating factor [MeSH], filgrastim [MeSH], placebo effect [MeSH], adult stem cells [MeSH], hematopoietic stem cell [MeSH], hematopoietic stem cell mobilization [MeSH] and $CD34^+$ cells [Free text]. Study designs searched were RCTs. Studies not utilizing a placebo drug in the control group were also included. Previous meta-analyses and review articles were analyzed for the identification of any additional studies.

Data collection and analysis. Potentially eligible studies were evaluated separately by two reviewers based on the inclusion and exclusion criteria. Following the removal of duplicates, studies were scrutinized by their titles and abstracts. The full-texts of selected articles were then scanned for inclusion in the review. Any difference in opinion was resolved by discussion. We extracted the following data from the included trials: Authors, publication year, inclusion/exclusion criteria, sample size, demographic data, plerixafor and G-CSF protocol, apheresis protocol, outcomes assessed and adverse events. The primary objective was to perform the quantitative analysis of successful optimal HSC mobilization. The secondary objectives were the following: The analysis of number of patients achieving minimal HSC mobilization, the quantitative analysis of the time required to achieve optimal and minimal HSC mobilization, the number of $CD34^+$ cells collected, the number of patients subsequently transplanted and adverse events.

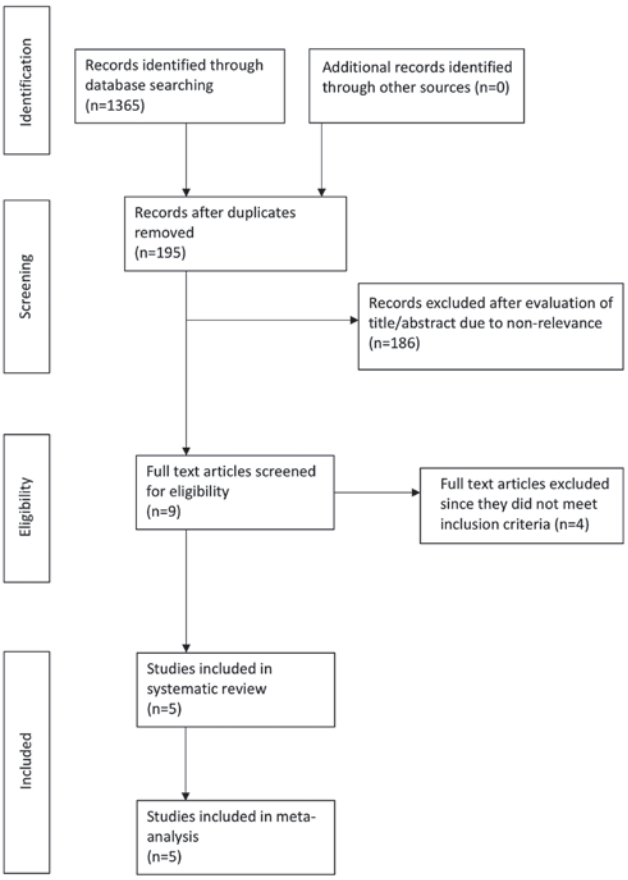

Figure 1. Flow chart of this study.

Risk of bias in individual studies. We assessed the risk of bias in each trial using the Cochrane Collaboration risk assessment tool for RCTs (18). Seven criteria were evaluated for each study: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases. Studies were scored for each criteria as follows: Low risk (score of 2), high risk (score of 0), or unclear risk of bias (score of 1). Based on the scores awarded, individual studies were grouped as low-(score 0-5), medium-(score 6-10), or high-(score 11-14) quality trials.

Statistical analysis. Meta-analysis was carried out only if at least 3 trials reported data on the same scale. The outcome data extracted was entered into Review Manager [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration)], Copenhagen, Denmark; 2014) for quantitative analysis. We used Intention to treat data from the trials for the purpose of analysis. Considering the heterogeneity amongst studies, a random-effects model was used to calculate the pooled effect size. Heterogeneity was calculated using the I^2 statistic. I^2 values of 25-50% represented as low, values of 50-75% as medium and >75% were represented as substantial heterogeneity. For binary outcomes,

Table I. Characteristics of included studies.

Authors/(Refs.), year	Diagnosis	No. of patients		Age (range/mean ± SD)		Sex: No. of patients		Remission status (n)		G-CSF protocol	Plerixafor protocol	Apheresis protocol
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control			
DiPersio *et al* (13), 2009	NHL	150	148	29-75	22-75	M: 100	M: 102	1st CR: 51 2nd CR: 30 1st PR: 26 2nd PR: 43	1st CR: 44 2nd CR: 29 1st PR: 19 2nd PR: 54	10 μg/kg SC daily in the morning for up to 8 days	Beginning on day 4, patients received either plerixafor 240 μg/kg or placebo SC daily in the evening for up to 4 days or until ≥5x10^6 $CD34^+$ cells/kg were collected	Apheresis began on the morning of day 5 and continued daily for up to 4 days or until ≥5x10^6 $CD34^+$ cells/kg were collected
DiPersio *et al* (12), 2009	MM	148	154	58.2±8.4	58.4±8.6	M:100	M:107	1st CR: 11 2nd CR: 129 1st PR: 0 2nd PR: 8	1st CR: 18 2nd CR: 126 1st PR: 0 2nd PR: 10	10 μg/kg SC daily in the morning for up to 8 days	Beginning on day 4, patients received either plerixafor 240 μg/kg or placebo SC daily in the evening for up to 4 days or until ≥6x10^6 $CD34^+$ cells/kg were collected	Apheresis began on the morning of day 5 and continued daily for up to 4 days or until ≥6x10^6 $CD34^+$ cells/kg were collected
Ri *et al* (19), 2017	MM	7	7	38-71	49-67	M:4	M:4	1st CR: 1 2nd CR: - 1st PR: 6 2nd PR: -	1st CR: 0 2nd CR: - 1st PR: 7 2nd PR: -	400 µg/m^2/day SC daily in the morning for up to 8 days	Beginning on day 4, patients in treatment group received plerixafor 240 μg/kg SC daily in the evening for up to 4 days or until ≥6x10^6 $CD34^+$ cells/kg were	Apheresis began on the morning of day 5 and continued daily for up to 4 days or until ≥6x10^6 $CD34^+$ cells/kg were collected
Zhu *et al* (14), 2017	NHL	50	50	18-66	20-60	M:31	M:26	1st CR: 21 2nd CR: 10 1st PR: 13 2nd PR: 5	1st CR: 22 2nd CR: 10 1st PR: 13 2nd PR: 5	10 μg/kg SC daily in the morning for up to 8 days	Beginning on day 4, patients received either plerixafor 240 μg/kg or placebo SC daily in the evening for up to 4 days or until ≥5x10^6 $CD34^+$ cells/kg were collected	Apheresis began on the morning of day 5 and continued daily for up to 4 days or until ≥5x10^6 $CD34^+$ cells/kg were collected
Matsue *et al* (15), 2018	NHL	16	16	39-73	27-70	M:11	M:12	1st CR: 3 2nd CR: 7 1st PR: 4 2nd PR: 2	1st CR: 10 2nd CR: 1 1st PR: 3 2nd PR: 2	400 µg/m^2/day SC daily in the morning for up to 8 days	Beginning on day 4, patients in treatment group received plerixafor 240 μg/kg SC daily in the evening for up to 4 days or until ≥5x106 CD34+ cells/kg were collected	Apheresis began on the morning of day 5 and continued daily for up to 4 days or until ≥5x106 CD34+ cells/kg were collected

NHL, non-Hodgkin lymphoma; MM, multiple myeloma; SD, standard deviation; M, male patients; n, no. of patients; SC, subcutaneously.

risk ratios (RR) with 95% confidence intervals (CI) were calculated. The mean and standard deviation (SD) scores of the number of $CD34^+$ cells collected were used for the meta-analysis.

Results

Search outcome. The search outcome of the review is presented in Fig. 1. A total of 195 articles were examined by their abstracts. In total, 186 studies were excluded due to non-relevance, leaving a total of 9 articles (12-15,19-23). Four studies were excluded from the review, as 2 were non-randomized (22,23), 1 had no control group (20) and 1 used a retrospective control group (21). A total of 5 trials were included in this systematic review and meta-analysis (12-15,19).

Characteristics of included studies and data analysis. Details of the included studies are presented in Table I. Three studies (12-14) were multi-center studies, while 2 were single-center trials (15,19). Three studies (13-15) were carried out on NHL, while 2 trials (12,19) were on patients with MM. Two trials [1 on NHL (15) and 1 on MM (19)] did not administer any placebo to the control group. The G-CSF protocol was standard across the studies, which consisted of subcutaneous (SC) injections in the morning for 8 days. Similarly, plerixafor was injected by SC injection in the evening, beginning on day 4 in all studies for up to 4 days and apheresis was carried out from the morning of day 5 and continued daily for up to 4 days or till the targeted HSC collection was reached. In the studies on NHL, the optimal HSC collection was $\geq 5x10^6$ $CD34^+$ cells/kg, while in the MM studies, it was $\geq 6x10^6$ $CD34^+$ cells/kg.

Data on successful optimal HSC mobilization i.e., the collection of $\geq 5x10^6$ $CD34^+$ cells/kg or $\geq 6x10^6$ $CD34^+$ cells/kg in ≤4 apheresis days was available from 4 included studies (Table II). From the pooling of the data of 364 patients in the treatment group and 368 patients in the control group, it was found that patients randomized to plerixafor had better successful HSC mobilization than those in the control group (RR=2.59, 95% CI: 1.40 to 4.81; P<0.0001; Fig. 2). There was significant heterogeneity (I^2=86%), which could be attributed to different underlying conditions or a different targeted stem cell number. Subgroup analysis based on diagnosis demonstrated a statistically significant improvement in optimal HSC collection in both the NHL and MM subgroup. Data on successful minimal HSC mobilization i.e., the collection of $\geq 2x10^6$ $CD34^+$ cells/kg in ≤4 apheresis days of 371 patients in the treatment group and 375 patients in the control group was also pooled for analysis. The results indicated that patients in the plerixafor group had better minimal HSC mobilization than those in the control group (RR=1.46, 95% CI: 1.01 to 2.12; P=0.04; I^2=94%; Fig. 3). Subgroup analysis based on diagnosis indicated a statistically significant difference in both the NHL and MM subgroups.

The number of days required to reach optimal ($\geq 5/6x10^6$ $CD34^+$ cells/kg) or minimal ($\geq 2x10^6$ $CD34^+$ cells/kg) HSC mobilization reported by the studies is presented in Table II. Since only median values were available, data could not be pooled for a quantitative analysis. The qualitative assessment of results from all 5 studies indicated that the addition of plerixafor significantly reduced the number of days required for the collection of optimal HSCs. Similarly, 4 (13,14,15,19) of the 5 included trials, which studied median time (days) required

Table II. Outcome assessment by included studies.

Authors/(Refs.),year	No. of patients able to mobilize ≥5/6x10^6 $CD34^+$ cells/kg in ≤4 apheresis days		No. of patients able to mobilize ≥2x10^6 $CD34^+$ cells/kg in ≤4 apheresis days		Median time (days) required to reach ≥5/6x10^6 $CD34^+$ cells/kg		Median time (days) required to reach ≥2x10^6 $CD34^+$ cells/kg		No. of $CD34^+$ cells/kg collected in 4 days of apheresis (mean ± SD)		No. of patients who underwent auto-HSCT		No. of adverse events (n/N)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
DiPersio *et al* (13), 2009	89	29	130	70	VNR	VNR	VNR	VNR	5.69 (±NR) x10^6	1.98 (±NR) x10^6	105	82	146/150	138/145
DiPersio *et al* (12), 2009	112	79	141	136	1	4	NS	NS	12.97 (±10.67) x10^6	7.31 (±5.49) x10^6	142	136	140/147	140/151
Ri *et al* (19), 2017	5[a]	0[a]	7	6	2	Not Reached	1	2	7.55 (±2.32) x10^6	3.67 (±1.25) x10^6	NS	NS	6/7	4/7
Zhu *et al* (14), 2017	31	10	44	33	2	Not Reached	1	2	NS	NS	44	34	32/51	31/49
Matsue *et al* (15), 2018	9	1	15	5	3.5	NR	1	VNR	5.45 (±2.55) x10^6	2.09 (±1.69) x10^6	NS	NS	13/16	12/16

VNR, values not reported; NS, not studied; n/N, no. of events/number of patients studied; Treat, treatment; Con, control. [a]Study endpoint was the collection of $\geq 6x10^6$ $CD34^+$ cells/kg in ≤2 apheresis days, hence not included in meta-analysis.

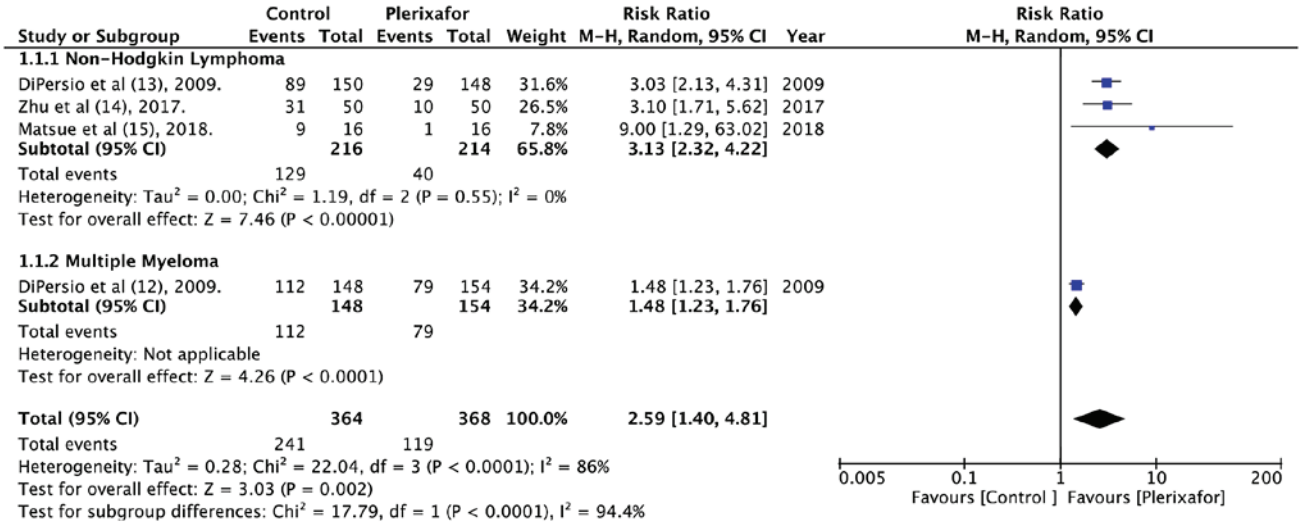

Figure 2. Forrest plot of non-Hodgkin lymphoma and multiple myeloma for the mobilization of optimal hematopoietic stem cells in 4 or less apheresis days.

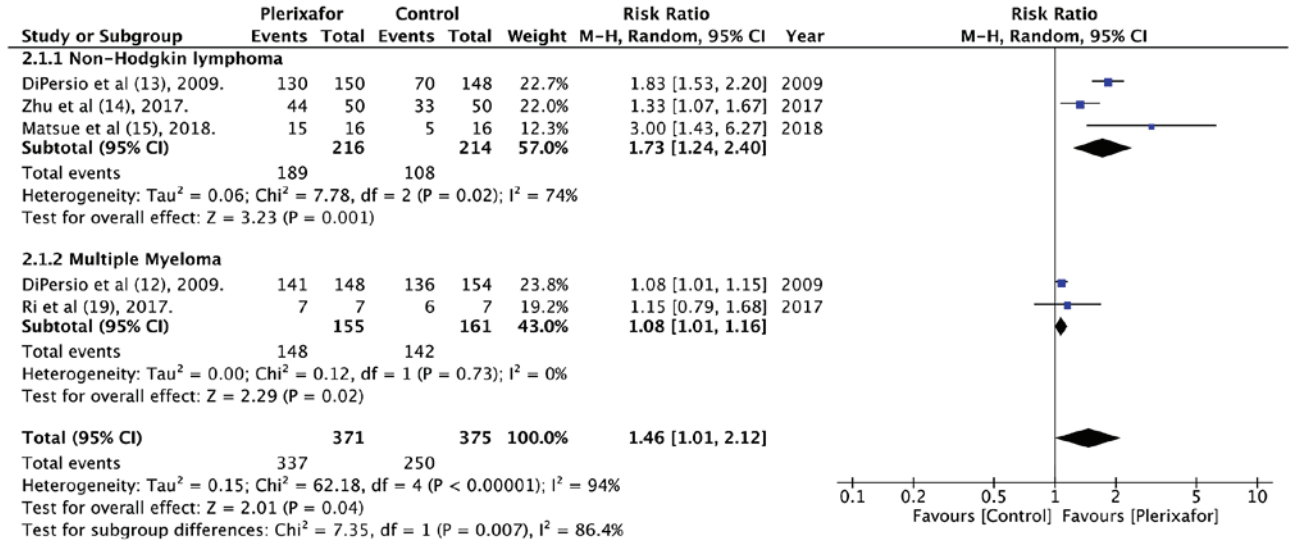

Figure 3. Forrest plot of non-Hodgkin lymphoma and multiple myeloma for the mobilization of minimal hematopoietic stem cells in 4 or less apheresis days.

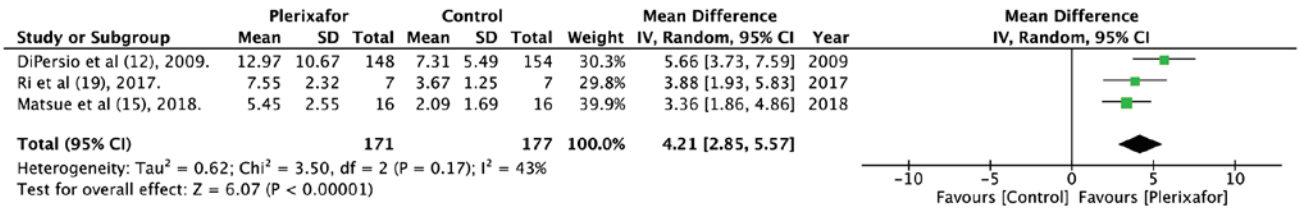

Figure 4. Forrest plot of mean total number of CD34+ cells collected in up to 4 apheresis days.

to reach ≥2x10^6 CD34$^+$ cells/kg, concluded that the number of days required for HSC mobilization to be less with plerixafor.

The mean total number of CD34$^+$ cells collected in up to 4 apheresis days was studied by 4 trials (12,13,15,19) (Table II). The data pooled from 3 studies (12,15,19) indicated that the addition of plerixafor significantly increased the total collection of CD34$^+$ cells (random: MD=4.21; 95% CI: 2.85 to 5.57; P<0.00001; I^2=43%; Fig. 4). In addition, a significantly greater number of patients randomized to plerixafor eventually underwent HSCT (RR=1.19, 95% CI: 1.02 to 1.39; P=0.03; I^2=70%; Fig. 5).

The numbers of patients experiencing at least 1 or more treatment related adverse events in both groups were pooled. The meta-analysis of 371 patients in the plerixafor group and 368 patients in the control group indicated no significant increase in adverse events with the addition of plerixafor (RR=1.03, 95% CI: 0.99 to 1.06; P=0.16; I^2=0%; Fig. 6).

Quality of included studies. The risk of bias summary of the included studies is presented in Fig. 7. The randomization method was not described in 2 studies (12,13) and 2 studies were not

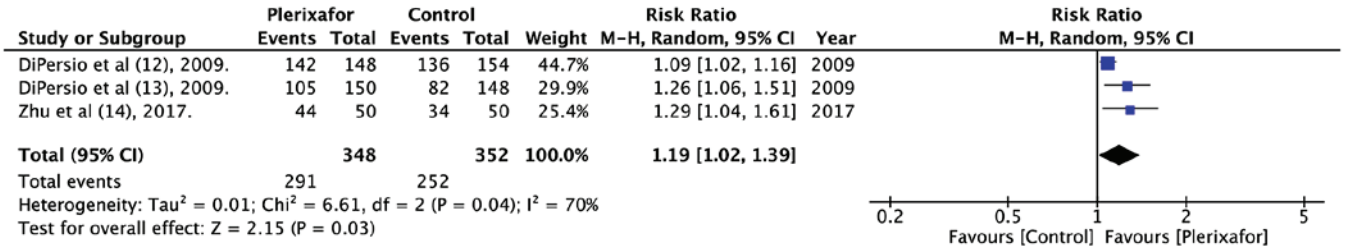

Figure 5. Forrest plot of the number of patients undergoing transplantation.

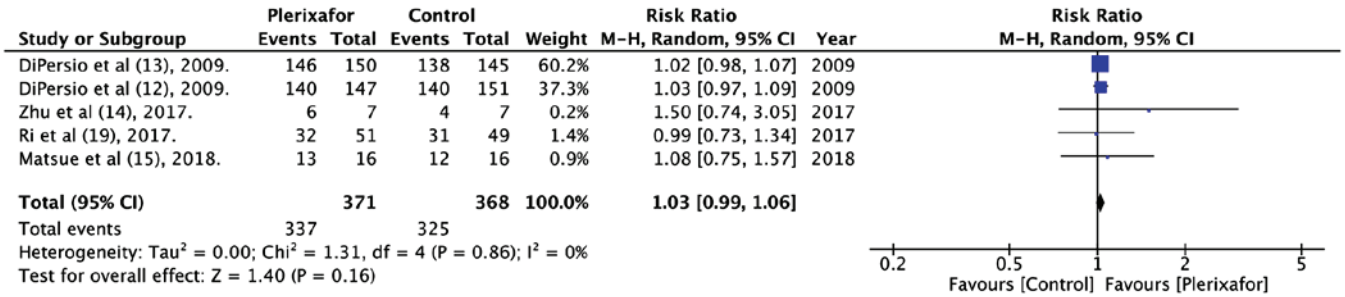

Figure 6. Forrest plot of adverse events.

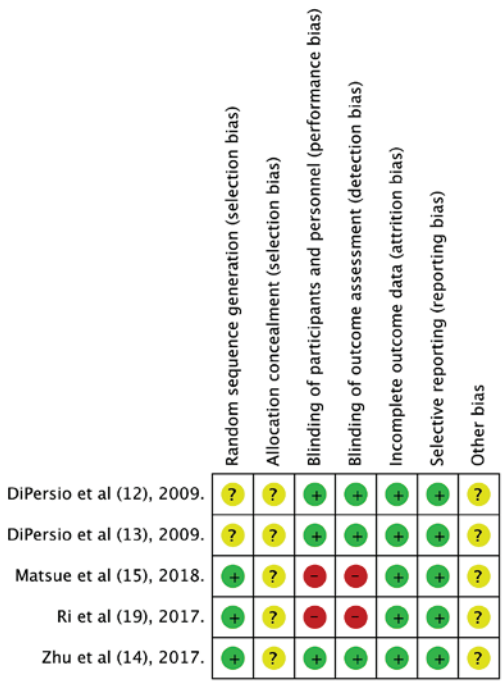

Figure 7. Risk of bias summary.

double blind (15,19). Since all studies had financial support from pharmaceutical companies, they were marked with 'unclear risk' for other sources of bias. The overall quality of the studies was rated 'high' for 3 trials (12-14) and 'medium' for 2 trials (15,19).

Discussion

In 2003, AMD3100, as plerixafor was formerly known, was studied by Liles *et al* (24) in healthy volunteers as a potential HSC mobilizer. The authors reported rapid generalized leukocytosis and an increase in the number of $CD34^+$ cells in peripheral blood with a single dose of the drug. Later, in their study, serial administration of the drug at 80 μg/kg/day for 3 days resulted in a consistent, reversible increase in the number of $CD34^+$ cells in peripheral blood with minimal toxicity. Their findings suggested the potential clinical application of plerixafor for HSCT. Their results were soon confirmed in patients with NHL and MM, where a significant increase in the $CD34^+$ counts was noted (25). Phase 2 trials later established the superiority of plerixafor + G-CSF as compared to G-CSF alone for autologous HSC mobilization (26). Superior evidence in the form of RCTs by DiPersio *et al* (12,13) paved the way for the approval of plerixafor by FDA in December, 2008 (27). The drug was ratified for use in patients with NHL and MM for the mobilization of HSCs for autologous transplantation. Since then, a number of studies have evaluated the role of plerixafor in patients with NHL and MM. Single arm prospective trials or retrospective studies form the bulk of the research conducted (28-30). The results of our systematic review indicated that 5 RCTs evaluating the role of additional plerixafor to G-CSF have been published to date. Three of these were conducted on NHL (13-15) and 2 on patients with MM (12,19). The study end-points were more or less similar across trials which enabled the pooling of the data for the purposes of our meta-analysis.

The minimum number of $CD34^+$ cells likely to result in successful engraftment is generally considered to be $\geq 2x10^6$ cells/kg, whereas the 'optimal' number of HSCs for transplantation is $4\text{-}6x10^6$ $CD34^+$ cells/kg (31). It has been found that the re-infusion of higher number of $CD34^+$ cells is associated with earlier engraftment following transplantation, with better disease-free and overall survival than lower cell doses (32). As a result, many transplant centers strive to harvest the optimal number of HSCs rather than the minimal dose. The primary efficacy end-point in the majority of the included trials of this review was the collection of optimal HSCs in 4 or less apheresis days. The results of our meta-analysis revealed that patients receiving additional plerixafor were 2.59-fold more likely to achieve optimal HSC collection in 4 or less apheresis

days. Similarly, patients in the plerixafor group were 1.46-fold more likely to mobilize minimal HSCs ($\geq 2x10^6$ cells/kg in 4 or less apheresis days) as compared to those receiving G-CSF only. There was slight variation in the primary efficacy end-point in NHL and MM studies, with NHL studies reporting the mobilization of $\geq 5x10^6$ cells/kg, while MM studies reporting the mobilization of $\geq 6x10^6$ cells/kg as the optimal number of HSCs for harvest. A higher primary endpoint is set for the collection of HSCs in patients with MM as they frequently require a second transplantation. A subgroup analysis was therefore carried out for NHL and MM, which demonstrated the effectiveness of plerixafor in both conditions. An important aspect to note is that only one study (12) was available evaluating the collection of optimal HSCs in 4 or less apheresis days for MM. The study by Ri *et al* (19) reported the collection of $\geq 6x10^6$ cells/kg in 2 or less apheresis days and was not pooled with the other study of DiPersio *et al* (12) for this variable.

In addition to the optimal collection of HSCs, another critical goal of stem cell mobilization is to collect cells in minimum number of days so as to reduce treatment stress and financial burden of the patient and also ensure optimal utilization of medical resources. Despite the fact that pooled analysis was not possible for the number of days needed for HSC mobilization with or without plerixafor, all studies included in this review reported the rapid mobilization with the drug. The median number of days for both optimal and minimal HSC mobilization was less with the addition of plerixafor. The more rapid collection of HSCs may lead to better patient compliance, reduce apheresis-associated risks and may shorten the interval between mobilization and transplant (15). The superior efficacy of plerixafor + G-CSF was also observed in the total number of $CD34^+$ cells collected and the number of patients who eventually underwent HSCT.

The safety profile of plerixafor was tested in all included studies. Based on our analysis and the investigation of individual trials, plerixafor is generally well-tolerated and there is no significant increase in treatment-related adverse events with the addition of the drug. In both the trials of DiPersio *et al* (12,13), the majority of adverse events were gastrointestinal (GI) disorders or injection site reactions. Ri *et al* (19) reported increased headaches, diarrhea and back pain with the addition of plerixafor. Zhu *et al* (14) and Matsue *et al* (15) reported GI-related disorders and headaches to be more common in the plerixafor arm than the control arm. All adverse events reported were mild to moderate and there were no treatment-related deaths reported in any of the included studies.

As plerixafor tends to mobilize relatively different cell populations as compared to other methods of mobilizing $CD34^+$ cells, post-transplant outcomes, such as hematopoietic and immune recovery and progression-free survival (PFS) are important variables of concern to clinicians (2). In total, 2 of the 5 included trials reported that engraftment and short-term outcomes at 12 months were similar with plerixafor + G-CSF and plerixafor + placebo. Importantly, the long-term results of these 2 studies have been published recently (33). The results indicated that the probability of overall survival and PFS evaluated over a period of 5 years did not differ significantly in patients with NHL or MM treated with plerixafor or the placebo. There is however, a need for more such long-term studies in order to validate the safety and efficacy of plerixafor for long-term PFS.

Some limitations of our review and meta-analysis need to be elaborated. Firstly, the paucity of RCTs limited the number of studies for inclusion in our review. Secondly, not all trials included were high quality studies. In total, 2 of the 5 included studies were sored as 'medium quality' based on the quality assessment tool. Thirdly, data on engraftment, long-term overall survival and PFS were not available from all included studies. Fourthly, as with any meta-analysis, heterogeneity as measured with I^2 statistic was significant in all our investigations. The time period, locations and samples of individual trials are quite variable across studies, but are usually balanced between the two arms of the meta-analysis. Nevertheless, our systematic review and meta-analysis is a significant update from the last review published on the subject by Hartmann *et al* in 2015 (11). Data from a 3 additional trials were available and added for quantitative analysis. The results of this study indicate that addition of plerixafor to G-CSF leads to increased HSC collection in a shorter period of time with no concomitant increase in adverse events. Further RCTs with a larger sample size evaluating short-term efficacy, as well as long-term survival would help to further strengthen evidence on this subject.

Acknowledgements

Not applicable.

Funding

This study was supported by the National Natural Science Funding Project (grant no. 8187014).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XY conceived and designed the study. MW, FY and ZW collected the data and performed the literature search. All authors were involved in writing the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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