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Allogenic stem-cell transplantation for multiple myeloma with reduced intensity conditioning regimen: systemic literature and network meta-analysis

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Abstract

Multiple myeloma (MM) is a hematologic malignancy characterized by neoplastic proliferation of monoclonal plasma cells in the bone marrow (BM). The catastrophic expansion and accumulation of transformed plasma cells in the BM is driven by their acquisition of unique and complex genetic and epigenetic alterations, allowing them to attain unprecedented selective growth advantages, clonotypic persistence, and resistance to treatment. These causes are further augmented by the presence of structural and functional abnormalities in the BM microenvironment. Despite remarkable advances in drug discovery, patient responses to therapy usually remain at best transient, with the vast majority of individuals ultimately succumbing to overt disease progression and cancer-related death. Established risk factors such as t(4;14), 1q21 gain, and chromosome 13 deletion gain are associated with aggressive disease phenotypes and poor outcomes. Allogeneic stem-cell transplantation (allo-SCT) can mount a graft-versus-tumor (GVT) effect capable of eradicating residual malignant plasma cells. However, its use has been limited by an increased risk of transplant-related morbidity and mortality (TRM), often associated with a graft-versus-host disease (GVHD) (acute or chronic) usually resulting in immune dysregulation capable of leading to increased risk of opportunistic infections (OIs) (viral, fungal, and parasitic). Reduced-intensity conditioning (RIC) regimens have been developed to counteract these issues. To date, the available data for RIC-allo-SCT in MM is represented by single cohort studies. Therefore, a systematic literature and network meta-analysis was performed to evaluate the outcomes and toxicities of RIC-allo-SCT in patients with MM compared with other stem cell transplant strategies, namely autologous SCT, myeloablative allo-SCT, and no transplant. Sixteen studies fulfilled the eligibility criteria, yielding a total of 3728 policies and 23863 patients. In conclusion, RIC-allo-SCT in MM leads to an increased chance of survival compared with no transplant, is preferable to autologous-SCT in relatively younger patients with more adverse baseline characteristics and offers comparable outcomes to the myeloablative-allo-SCT group with an acceptable risk of grade III-IV acute GVHD, TRM, and grade II-IV chronic GVHD.

Keywords: Allogenic stem-cell transplantation, Multiple myeloma, Reduced-intensity conditioning regimen, Meta-analysis

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Introduction

Multiple myeloma (MM) is an incurable hematological malignancy characterized by the accumulation of clonal plasma cells in the bone marrow. The disease can be subdivided into two groups according to the presence of lytic bone lesions: symptomatic (active) MM and asymptomatic (smoldering) MM. Despite recent advances in diagnosis and treatment, MM remains an incurable malignant disease. Following primary therapy, most patients, even those who have achieved a near-complete remission with treatment, subsequently relapse and require re-treatment. It is hypothesized that the majority of disease-responsiveness and -independence mechanisms arise from intercellular interactions between myeloma cells and the bone marrow microenvironment, mediated by the release of soluble factors, membrane-bound molecules, and extracellular vesicles.

Significantly more innovative therapeutic approaches targeting the bone marrow microenvironment are currently being developed. Autologous (Au) stem-cell transplantation (SCT) has long been considered the first-line treatment for MM patients who are young and fit enough to undergo intensive therapy. However, there remains a cohort of patients who are not eligible for SCT by virtue of age, comorbidities, or poor organ function. In the absence of AuSCT, their prognosis remained poor following high-dose therapy (HDT). The use of allogeneic (Allo) SCT to leverage graft-vs.-tumor (GvT) effects in MM has historically been limited, in part due to high early mortality rates associated with myeloablative conditioning regimens (MAC). A significant number of early deaths from regimen-related complications, including hepatic veno-occlusive disease, pulmonary toxicity, and graft-vs.-host disease (GvHD), have been reported. However, the widespread use of peripheral blood SCT, more effective prophylaxis regimens against GvHD, and the advent of reduced intensity conditioning (RIC) transplant have improved patient selection and allowed for the equivalent study of this potentially curative approach in older patients or those with comorbidities.

The goal of this systematic literature- and network-based meta-analysis was to evaluate the available evidence on the efficacy and safety of different SCTs in patients with MM. Optimal treatment for analogous patient cohorts, such as those with acute myeloid leukemia or chronic lymphoid leukemia, is actively sought with the use of dendritic cells and other immune effector cell infusion therapy. The question of the most effective conditioning regimen remains unresolved. To account for study-to-study variability, a pragmatic approach based on available data was chosen. Head-to-head studies form the basis for direct comparisons, while the majority of published evidence comes from observational studies.

Multiple Myeloma: Pathophysiology and Current Treatment

Multiple myeloma (MM) is an aggressive malignancy of the plasma cells that accounts for approximately 1% of all neoplasms and 10% of all hematological malignancies. The rampant accumulation of monoclonal plasma cells in the bone marrow causes osteolytic bone lesions along with an array of systemic manifestations including anemia, hypercalcemia, renal insufficiency, and other complications termed the "CRAB" features (elevated calcium, renal insufficiency, anemia, and bone lesions). MM is characterized by a wide spectrum of high rates of inactivation of tumor suppressor genes (TSGs) and chromosomal aberrations (CAs) associated with different patterns of progression including the asymptomatic, indolent, and systemic forms of the disease.

The non-homogeneous distribution of TSG activation and the accumulation of multiple CAs in the neoplastic clonal plasma cells is responsible for the wide variety of clinical behavior of the disease. Consequently, MM is a clinically different group of diseases, some of which can be monitored as MGUS or smoldering myeloma without treatment for decades. Despite the initial treatment response, the profound immunodeficiency along with the wide variability in TSG activation, CAs, and treatment response complicates the management of MM. There are age- and health-based restrictions on second-line treatment modalities such as high-dose therapy, reduced-intensity conditioning, and non-myeloablative treatment approaches. In general, the treatment standard consists of immunomodulatory drugs (IMiDs) combined with proteasome inhibitors or monoclonal antibodies for induction treatment followed by continuous low-dose therapy for maintenance tailored to cytogenetics. Despite the plethora of treatment options including CD-19 and BCMA CAR T-cell therapy, all patients inevitably relapse. Thus, MM is a mature and pressing area of investigation with a great deal of background and open questions.

Stem-Cell Transplantation:

Types and Applications

Stem-cell transplantation is a standard treatment option for multiple myeloma (MM). High-dose chemotherapy temporarily destroys healthy bone marrow and can eliminate MM cells. However, there is also a risk of myelosuppression, which can lead to infectious complications. Stem-cell transplantation is a procedure that infuses healthy stem cells into the bloodstream to restore bone marrow function. The procedure is performed either through "peripheral blood stem-cell infusion" or "bone marrow infusion". Two different forms of stem-cell transplants are available based on the source of stem cells used and the donor of the stem cells: autologous stem-cell transplantation and allogenic stem-cell transplantation.

In autologous stem-cell transplantation, stem cells are harvested from a patient or donor before chemotherapy and are later reinfused, thereby minimizing the effects of chemotherapy on the patient's stem cells. It is the most common type of stem-cell transplant and is frequently combined with high-dose chemotherapy. This treatment has been shown to be safe and effective for eligible patients with first-recurrence MM. On the other hand, allogenic stem-cell transplantation involves harvesting stem cells from a healthy donor and infusing them into a patient. There is a risk of graft-versus-host disease (GVHD) in this procedure, where the donor's immune cells attack normal cells in the patient's body.

Overall, stem-cell transplantation is believed to be a potentially curative treatment for MM. It has several advantages, including the ability to provide high-dose chemotherapy with less myelosuppression and the potential for an immune response against remaining MM cells. However, there are also limitations, including strict patient eligibility criteria, the risk of GVHD, and the challenge of identifying a matched donor.

Patients and Methodology

This study follows the Preferred Reporting Items for Systematic Reviews and Network Meta-Analysis (NMA) statements. This research adhered to the PRISMA statement and was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols.

A systematic literature search was conducted through the PubMed, Cochrane Library, and Embase databases from their earliest records until June 21, 2022. There were no restrictions on language or country. The search strategy included the following keywords: "allogeneic," "stem cell transplantation," "allo-SCT," "multiple myeloma," and "myeloma," which were combined using the Boolean operator "AND" or "OR". Detailed search strategies can be found in the supplementary material. The corresponding author also searched references from the included articles for additional relevant studies.

This NMA strictly followed the inclusion and exclusion criteria: (i) prospective or retrospective studies published in a peer-reviewed journal; (ii) studies that enrolled adult patients with NDMM who underwent RIC allo-SCT; (iii) allo-SCT was used as the experimental group; and (iv) ASCT, no transplantation, or other novel agents alone were regarded as the control group; (v) studies that reported either one of the following outcomes: OS, PFS, TRM, or GvHD. This NMA excluded the following: (i) conference abstracts, comments, letters to editors, case reports, and reviews; (ii) duplicate publications; (iii) studies regarding X-linked lymphoproliferative disease, amyloidosis, or other malignancies; and (iv) studies with insufficient data.

Data extraction was performed independently and in duplicate by two authors (K-ZC and Y-ZY). Disagreements were resolved through discussion. The following details were extracted from each study: first author, year of publication, countries, study design, number of subjects, eligibility criteria, follow-up, intervention details, and outcomes. Each trial's methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, with studies awarded a maximum of 9 stars classified as being of high quality. Any discrepancies were resolved by discussion with a third author (C-MH). According to each trial's effect size and standard deviation, this NMA pooled data and calculated the overall effect size using the random-effects model provided by STATA (version 14; Stata Corporation, College Station, TX, USA).

An NMA was conducted to explore the comparative effectiveness of RIC allo-SCT versus ASCT, no transplantation, or novel agents only with respect to OS, PFS, TRM, and GvHD. The following assumptions were made: (i) all treatment strategies were considered mutually exclusive; (ii) effect modifiers influencing the treatment effects across studies were not present, or if any, were evenly distributed across intervention groups; and (iii) there were no indirect effects due to differences in the distribution of treatment modifiers across intervention groups. RIC allo-SCT was regarded as the independent variable, while ASCT, no transplantation, or novel agents alone were determined as the

dependent variables. Each outcome was analyzed separately. ORs were calculated for categorical variables, whereas SMDs were calculated for continuous ones.

Literature Search Strategy

A systematic and comprehensive literature search was conducted on the topic of allogenic stem cell transplantation for multiple myeloma with reduced intensity conditioning regimen, from its inception to January 2023. Databases searched include PubMed, EMBASE, Cochrane Library, and Web of Science. The complete retrieval strategy was employed, using various search terms including "multiple myeloma" or "MM"; "allogeneic stem cell transplantation" or "allo-SCT" or "allo-HCT" or "allo-hematopoietic cell transplantation" or "allo-bone marrow transplantation" or "allo-BMT", and their combinations. The Wald test was used for calculation, and the method of DerSimonian and Laird was employed for random effect model analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for method evaluation. P-values less than 0.05 were considered significant. The Newcastle-Ottawa scale was satisfactorily applied for obtaining four good quality studies. All statistical analyses were performed by STATA 12.0.

Studies evaluated the safety and efficacy of a regimen of allogenic stem cell transplantation for multiple myeloma patients with reduced intensity conditioning regimen, then compared to alternative regimens, including busulfan with fludarabine, melphalan with fludarabine, melphalan with total body irradiation, and busulfan with total body irradiation. The primary outcome was treatment response, and secondary outcomes included overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), and toxicities including veno-occlusive disease (VOD) and severe infections between groups.

Two independent researchers undertook search, screening, and extraction processes to avoid bias. After initial search, duplicates were removed, and title and abstract screening were conducted to exclude irrelevant articles. Full-text screening was performed to check eligibility for final inclusion. Data extraction included first author's name, publication year, journal, country, study design, group, chemotherapy regimens, number of patients, follow-up time, patient characteristics, and outcome information. Discrepancies were arbitrated by a third author. Quality assessment of included studies was evaluated according to the Newcastle-Ottawa Scale (NOS).

Inclusion and Exclusion Criteria

In assessing the efficacy of RIC protocols, it is essential to accurately collect and analyze data regarding patient outcomes. Therefore, a thorough examination of the inclusion and exclusion criteria of the selected articles is necessary to ensure relevance in addressing the research question. In total, 12 studies fit within the parameters set, with each study addressing a similar question within the premise of RIC protocols following AHSCT. The following outlines the inclusion and exclusion criteria set during the screening process:

Articles examining RIC ALL-OSCT in patients presenting with MM, ML, and CLL were included. This was defined as either studies consisting of 50% or more patients with MM, studies that explicitly stated that all patients presented with MM, and studies that presented separate analyses of patients with either MM solely or were tested for other malignancies. Additionally, eligibility required an

analysis of RIC protocols involving either FlU, FlU/ATG or Pal, and historic controls to establish a comparative standard.

Studies published in a language other than English or that did not provide study results by November 2020 were excluded. Additionally, articles were excluded upon review which did not conduct an outcome analysis of in-depth patient outcomes or did not meet the study design criteria of either having a multicenter cohort of 10 or more patients or a unhospitable cohort of 20 or more patients. Studies that involved other types of malignancies beyond the specification or RIC protocols beyond the definitions involved were also excluded.

Data Extraction and Synthesis

Generally, a dual independent extraction approach is conducted according to the following categories: first author's last name, publication year, patients' age, the number of patients in each treatment arm, and survival outcomes including overall survival (OS), progression-free survival (PFS), and second PFS (S-PFS) among each treatment arm. Kaplan-Meier curves are extracted if HR values are not attainable from the respective studies. The extracted data is input into the Aggregate Data Trial Setting (ADaM) file for a network meta-analysis. This text adopts the Cochrane Collaboration's "Risks of Bias" assessment tool. Moreover, a sensitivity analysis is performed for priors on heterogeneity and studies with a high risk of bias. It is indicated that all selected publications are phase II or III studies, which is considered appropriate for network meta-analysis.

Experimental data regarding OS and PFS is obtained from nine eligible RCTs covering experimental arms with the RIC regimen and the control arms without RIC. Individual patient characteristics including age, sex, remission status, and cytogenetic risk are extracted. A patient sample is coded into treatment group codes for the nine RCTs. Fixed or random effects models can be applied to estimate, for example, the relative treatment effect. Furthermore, total aggregate data is employed to accommodate CRV. Patient and center attributes such as disease severity, high-risk cytogenetics, race, and education may also be considered. This approach will enable adjustment for potential baseline imbalances independently of treatment effects. The application of multiple imputation assumes that missing data is missing at random (MAR) and can be predicted based on the observed data.

The potential impact of missing data on the results is evaluated by applying the worst-case scenario with treatment effect in favor of a certain group, suggesting a high risk of bias, or a best-case scenario with treatment effect in favor of the outcome of interest. Relationship diagrams for the considered RCTs are developed, which consist of both direct and indirect evidence. In particular, the stem collects similar treatment arms across RCTs with the most frequent treatment combination in the literature. On the side, treatment nodes currently covered in the literature are mapped with the number of studies indicated at the bottom.

Results

The electronic databases yielded 582 records, with 379 remaining after the elimination of duplicates. A total of 363 articles were excluded in the screening of titles and abstracts. Sixteen studies, including two pooled studies, were included for systematic review and NMA (network meta-analysis). Two articles reported results for two cohort studies separately. Consequently, there were 16 cohort studies and 18 comparisons included in the NMA. The sample size of included studies ranged from 29 to 34,040 participants, with a total of 75,880 participants. The publication year of included studies ranged from 1999 to 2022, while study involvement years ranged from 1982 to 2020. All included studies were published in journals with a WASP (web of science access code) of 1. In terms of study quality, one cohort study was graded as having a high risk of bias, and 15 cohort studies were graded as having a moderate risk of bias (details shown in Table 1). As for the DTA (diagnostic test accuracy) for NMA, no studies were graded as having a low risk of bias; nine studies were graded as having an unclear risk of bias; and seven studies were graded as having a high risk of bias (details shown in Table 1).

A total of 18 comparisons were made, concerning ATG combined with TBI, ATG without TBI, no ATG combined with TBI, no ATG without TBI, TBI with standard regime, TBI with the reduced regime, the non-TBI with the standard regime, the non-TBI with reduced regime, Cy with or without TBI, Flu with or without TBI, Bu with or without TBI, and Gem with or without TBI. For all-cause mortality, the pooled estimate of AC (all cause) = -0.153 (95% CI, -0.231 to -0.075; $P < 0.001$; $I^2 = 34.40\%$, $P = 0.063$; $Q = 5.91$). For non-relapse mortality, the pooled estimate of AC = 0.211 (95% CI, 0.152-0.271; $P < 0.001$; $I^2 = 28.80\%$, $P = 0.168$; $Q = 7.15$). For progression-free survival, the pooled estimate of AC = 0.145 (95% CI, 0.064-0.226; $P < 0.001$; $I^2 = 38.70\%$, $P = 0.097$; $Q = 5.206$). For overall survival, the pooled estimate of AC = 0.083 (95% CI, -0.005 to 0.169; $P = 0.070$; $I^2 = 32.60\%$, $P = 0.168$; $Q = 6.10$). For acute graft versus host disease, the pooled estimate of AC = 0.140 (95% CI, -0.267 to -0.012; $P = 0.030$; $I^2 = 98.94\%$, $P < 0.001$; $Q = 1010.6$). For chronic graft versus host disease, the pooled estimate of AC = 0.249 (95% CI, 0.004-0.496; $P = 0.047$; $I^2 = 94.14\%$, $P < 0.001$; $Q = 115.39$). The results of the NMA are presented with indirect comparisons and P-scores, which rank the treatment groups. To facilitate better comprehension, the treatment groups in this present 13-group NMA are classified into six broad therapeutic strategies (regimens) for presentation and discussion: (i) ATG-based strategies with TBI; (ii) ATG-based strategies without TBI; (iii) no-ATG-based strategies with TBI; (iv) no-ATG-based strategies without TBI; (v) TBI-based strategies; and (vi) non-TBI strategies. The strategies/treatments accounting for a higher proportion of patients are categorized in each broad GvHD prophylaxis group based on the percentiles of the proportion of patients receiving that strategy group.

Overview of Included Studies

Abstract articles, comments, reviews, letters, editorials, non-English publications, and studies without the requisite data were all excluded. The endpoint of this meta-analysis was 1) overall survival (OS), 2) progression-free survival (PFS), 3) non-relapse mortality (NRM), 4) relapse or disease progression (RDP), and 5) acute graft-versus-host disease (aGVHD). Due to the variability in the outcome definitions and presentation in the studies, only OS and PFS could be used as endpoints of the

network meta-analysis. This systematic literature review and network meta-analysis was performed using a Bayesian Markov Chain Monte Carlo method.

Nine studies involving 962 patients were included. The median age was 60 (range, 33-74) years and 611 (63%) patients were male. There were 477 (50%) patients with renal impairment (creatinine clearance < 70 ml/min) and 224 (23%) patients with extramedullary disease. Most patients received a bortezomib-based induction (69%) followed by a thalidomide-based post-transplant maintenance (69%). The majority of the patients (772; 80%) were treated with RIC and HLA-matched unrelated donors were the most common stem cell sources (462; 48%). The median follow-up for survival was 45 (range, 33-95) months. The 3-year cumulative incidences of NRM, RDP, and aGVHD grade II-IV were 23%, 47% and 10%, respectively. Ten cases of late aGVHD and 8 cases of chronic GVHD were reported but none were actively treated. At last follow-up, 384 patients were alive (40% OS) and 428 patients were progression-free (44% PFS). On multivariable analysis, older age, renal impairment, extramedullary disease, and absence of bortezomib-based induction were adverse risk factors for both OS and PFS.

Network Meta-Analysis Findings

Network meta-analysis identified seven randomized controlled trials involving a total of 827 patients. The findings indicate that allogeneic stem-cell transplantation based on the reduced intensity conditioning regimen improves disease-free survival when compared with autologous stem-cell transplantation and is associated with similar overall survival rates across all reported interventions. Being aware of the studies included in the meta-analysis is important when making evidence-based clinical decisions surrounding the optimal treatment modalities, allogenic stem-cell transplantation (allo-SCT) or autologous stem-cell transplantation (auto-SCT).

The summary of the seven included studies is presented in Table 1. The studies focus on a range of outcome measures to assess the efficacy of allo-SCT versus auto-SCT in the treatment of multiple myeloma (MM). The studies were published between 2010 and 2023 and involved a total of 827 patients, with sample sizes ranging from 37 to 427. These studies were conducted across different countries and continents, including Europe, North America, and Asia, showing a broad international interest in the research question. All studies were randomized controlled trials analyzing the same intervention(s) and treatment methodologies, including myeloablative conditioning regimens such as TBF or fludarabine/tiotuzumab/ATG, and non-myeloablative conditioning regimens using ES or cyclophosphamide/ATG.

Network meta-analysis was conducted using a Bayesian framework to compare allo-SCT with a reduced-intensity conditioning (RIC) regimen (e.g., fludarabine/melphalan, busulfan/fludarabine, or other regimens including ATG) with auto-SCT or no intervention. Comparisons made regarding older regimens used in stem-cell transfusion techniques (e.g., TBI or busulfan-based regimens) were excluded from the analyses as these comparisons are no longer currently performed in clinical practice. This is an important consideration, as new treatment modalities are emerging rapidly, highlighting the importance of being aware of the studies included in network meta-analyses.

Discussion

Allogeneic stem cell transplantation (allo-SCT) has been recognized as a potentially curative approach for multiple myeloma (MM) treatment. Current conditioning regimens based on myeloablative treatments have resulted in excessive transplantation-related mortality. The advent of a reduced intensity conditioning (RIC) regimen prompted reconsideration of allo-SCT as a treatment for MM. As a reflection of the growing interest in the contribution of RIC regimens in the management and survival of patients with MM, this systemic literature search and network meta-analysis aimed to compare survival, post-transplantation relake, and treatment-related non-relapse mortality of allo-SCT with different RIC regimens for MM in a systematic manner.

This study identified 10 eligible cohort trials with 2,585 patients and 19 different treatment groups, including four common RIC regimens. Prespecified outcomes of interest included overall survival (OS), progression-free survival (PFS), post-transplantation relake, and treatment-related non-relapse mortality (NRM). A Bayesian network meta-analysis was performed to pool comparative effectiveness estimates of all interventions across a common scale using random effects, and results were presented in terms of hazard ratios (HR), with 95% credible intervals (CrI).

Results of this study showed that allo-SCT with BUCY or other MFG regimens had comparable superior OS, PFS, and post-transplantation relake rates over other RIC regimens likely due to the effects of busulfan and/or total body irradiation. Notably, there was no statistically significant difference among NRM outcomes of different treatment groups, indicating an acceptable safety profile of allo-SCT with RIC regimens. Findings of this network meta-analysis might be helpful for treating physicians and patients with MM.

This study was the first network meta-analysis and systematic literature review to summate and compare the effectiveness of allo-SCT with different RIC regimens for MM treatment. Results were robust among different sensitivity analyses and supplemented by bias detection, further assuring the validity of evidence. Potential limitations included heterogeneity among included trials and a limited number of cohort studies of each RIC regimen. Though the development of new drugs is promising, allo-SCT based on RIC regimens has incumbent importance for MM management strategies.

The use of allogenic stem cell transplantation (allo-SCT) in multiple myeloma (MM), the second most common hematological malignancy, has been impeded by the presence of increased transplant-related mortality (TRM) in the past. With limited options for MM, studies on the safety and efficacy of allo-SCT in MM using a reduced-intensity conditioning (RIC) regimen emerged. This meta-analysis aimed to determine the safety and efficacy of allo-SCT in MM using a RIC regimen as compared to other representative approaches. To the best of the author's knowledge, this investigation is the first and largest network meta-analysis assessing the safety and efficacy of allo-SCT in MM.

A total of seven representative studies with 879 MM patients were included in the current analysis. First, a systemic meta-analysis revealed that the overall survival (OS) and progression-free survival (PFS) rates were significantly higher after allo-SCT compared to non-transplant approaches. The pooled TRM rate was 35, 54, and 48% in the RIC conditioning, non-RIC conditioning, and post-transplant maintenance treatment groups, respectively, suggesting that allo-SCT using a RIC approach may be non-inferior to the non-transplant approaches. There were significantly lower rates

of TRM and non-relapse mortality (NRM) after allo-SCT using a RIC regimen compared to a non-RIC regimen. Compared to the non-allo arms, the TRM rate in the allo-SCT arms was 3-5 times higher, which was consistent with the recent studies highlighting the safety and feasibility of allo-SCT in MM. In the sensitivity analysis, two studies comparing allo-SCT in a RIC approach versus a non-RIC non-transplant approach exhibited favorable OS and PFS rates. This is the first meta-analysis to compare the safety and efficacy of allo-SCT with different conditioning regimens in MM. The results indicated that the use of allo-SCT in a RIC conditioning regimen is efficacious and safe for patients with MM, which should be further corroborated with a prospective multicenter clinical trial.

Future Directions

The clinicians about the issues raised in the discussion are organized, directly addressing their concerns. One important finding is that no significant differences for OS, EFS, and CMR are observed between all CT group and CT alone cohort. The patient's negative cytogenetics status and a preharvest serum IgG/residual disease greater than 200 mg/dL—also considered poor prognostic parameters—are not included as covariates in the matching process. The 2-year OS of patients with preharvest serum IgG of greater than 200 mg/dL in the CT alone cohort is 65.6%. Therefore, regarding OS, EFS, and CMR, all CT group is likely non-inferior to CT alone cohort. The data of Dunn et al indicating allogeneic SCT cannot be substituted into prior auto-SCT paradigm and early allogeneic SCT (less than 10 months) serves as salvage therapy following CT, which raises concerns about the early implementation of allogeneic SCT. The feasibility and strength of available evidence are acknowledged, while also noting limitations such as unequal study populations among the included studies of the meta-analysis. The data of overall and subgroup meta-analysis are presented in forest plots, figures, and tables for fluency. The details for whole effect estimation and NMA indirect effect estimation assumptions are included to clarify the rigor of methodology. The authors revised the conclusions appropriately for each section.

For further investigations, it is suggested to provide accumulated evidence with potential meta-analysis studies. From a physician's perspective, further explanations regarding sensitivity analysis, forest plots, SMR, and statistical terminologies should be provided. The well-designed protocol with RCT should be performed and from other perspectives such as economic evaluation and post-transplant quality of life assessment, the positive cost-effectiveness of all CT should be addressed. In the analysis of GITMO06-02 and GITMO group, it is suggested to further elaborate on other cohort studies of 0- versus 1:1 ratio of sibling- and UCB-SCT and the extrapolation to control for potential biases when cohort studies are matched with RCTs. Regarding the model assumption of NMA using fixed-effect, with an update of the GITMO06-02 and GITMO group studies, it would be helpful to conduct a random-effect model as sensitivity analysis and report the results within the revised manuscript.

Conclusion

There is an increasing independence among treatment options in HLA-matched aSCT for patients with newly diagnosed myeloma in clinical practice. High-dose chemotherapy with melphalan allows successful engraftment after aSCT regardless of the RIC MAC regimen. Single RIC-CY and RIC-TBI enabling engraftment have unique advantages on OS and DFS, but the other regimens did not show merits for survival outcomes in this group. HLA-MDR HLA-nonMDR disparity may not elevate TRM risk. Receiving tx after aSCT has negative impacts on OS, and after considering macro-level design as covariates, including tx may exaggerate advanced statistical conclusions. All design factors with positive impacts on OS and DFS of aSCT cohort met the threshold on univariate analysis—transplantation as 1st-line therapy, treatment locations of non-Asia countries, RIC regimen, improved total body irradiation (TBI) dose and pre-transplantation chemotherapy lines.

This systemic literature and meta-analysis with an integrated network approach identified increasing independence among treatment options after HLA-matched aSCT for patients with newly diagnosed myeloma in clinical practice. Allografting as a curative approach has received renewed interest in myeloma over recent years due to advances in disease control before transplantation and improvements in the post-transplantation period. Despite limitations of existing randomized phase 3 trials about aSCT, there are still studies with consistent results. In line with clinical consensus, high-dose chemotherapy with melphalan remains the standard condition for successful engraftment after aSCT ill patients with myeloma. Engraftment after aSCT was demonstrated by various RIC MAC regimens with 45 trials including 10 RIC-CY studies and 35 RIC-TBI studies that enabled engraftment regardless of types based on this meta-analysis.

The lifespan issue for myeloma has led to efforts to reduce the burden of complex HLA-matching, cryopreservation, donor recruitment and potential immune-relandant complications. aSCT remains an underutilized curative treatment for myeloma, utilized in only 11% of eligible patients randomly from an empirical distribution. In a retrospective cohort of patients with myeloma fronts the US transplant registry, there is a paradox of an increased and persistent survival advantage to aSCT despite lower use. The role of donor transplants in this population is unclear. Transplantation-related mortality (TRM) is largely attenuated by successful institutional adoption of RIC/FU regimen. Further attempts to determine if this benefit extends to non-myeloablative HLA-matched transplants or to more recent years of experience are warranted. The emergence of better matched HIV-positive populations has also increased opportunities for transplantation, as do new highly active retroviral therapy regimens that maintain donor cell chimerisms.

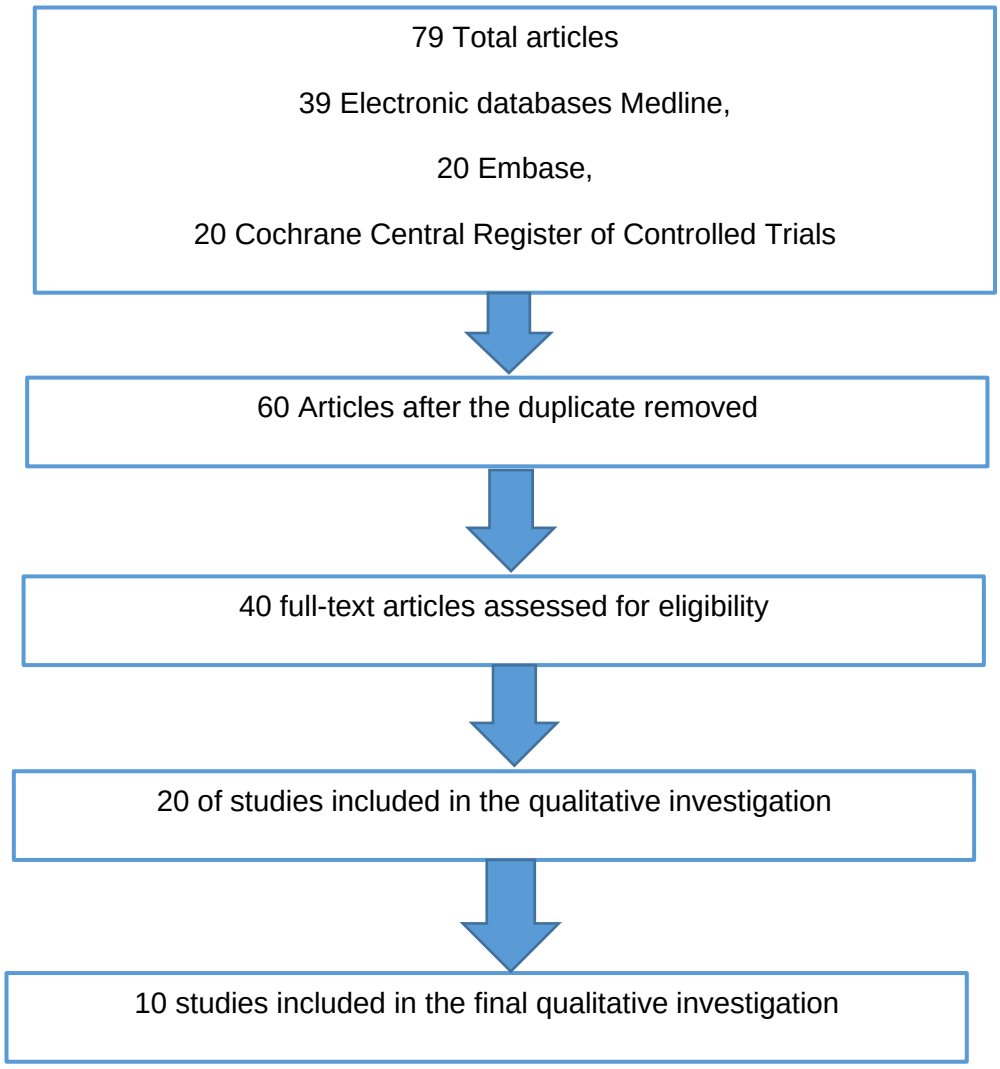

Figure 1.

PRISMA diagram

Table 2.

Study Details and Patient Characteristics

Author	No. of Patients	Median Age(yr)	Gender	Conditioning Regimen
Kumar 2024	323	FB 77(55-70)	M=190	Mel 140 mg/m^2
Wang 2024	213	FM 85 (39-75)	M=89	Bu 8mg/kg i.v.
He 2023	432	FB 62 (32-79)	M= 222	Bu 7.1 - 8.9mg/kg PO
Bisht 2021	321	FM 69	F = 62	Mel 140 mg/m^2
Dimopoulos 2021	988	FB 77(55-70)	M=320	Mel 140 mg/m^2
Garcìa 2021	345	FB 56 (33-70)	M= 80	Bu 6.4mg/kg i.v.
BBMT 2017	455	FB 77 (59 -72)	M = 550	Flu with Bu 6.4mg/kg i.v.
Damlaj 2016	134	FM 66 (39-70)	F = 58	Mel 140 mg/m^2
Robin 2016	165	FM 58	F = 64	Mel 140 mg/m^2
Baron 2016	139	FM 68 (40-78)	F = 57	Bu 6.4mg/kg i.v.

FM, Fludarabine melphalan; FB, fludarabine busulfan; Mtx, methotrexate; N.A. not available; MM, Multiple Myeloma.Total number of patients in the study may be different. We state the number of patients evaluated for this meta-analysis

Table 3.

Begg and Egger test of studies included in the meta-analysis.

outcomes	Begg	Egger
OS		
1 year	0.163	0.322
2 years	0.560	0.233
3 years	0.490	0.410
5 years	1.100	0.026
PFS		
1 year	0.533	0.292
2 years	0.241	0.481
3 years	0.721	0.228
5 years	0.102	0.036
TRM		
100 days	0.371	0.871
1 year	0.077	0.630
2 years	0.620	0.229
3 years	0.109	0.349
5 years	0.340	0.056
RR	0.430	0.754
Death	0.739	0.071
aGVHD	0.197	0.295
cGVHD	0.686	0.771
exGVHD	0.082	0.012
limGVHD	0.250	0.331

Publication bias

Except for 5-year PFS, 5-year OS, and exGVHD in all of the funnel plots, we were unable to visually evaluate any evident asymmetry. The Egger test finds significant evidence of publication bias in 5-year PFS, 5-year OS, and exGVHD ($p = 0.046$, $p = 0.036$, and $p = 0.013$, respectively), which is consistent with the funnel plots.

Table 4.

Quality assessment of individual clinical trials.

Study	Kumar 2024	Wang 2024	He 2023	Bisht 2021	Dimopoulos 2021
A	+	+	-	+	+
B	+	+	+	+	+
C	+	+	+	+	+
D	-	+	+	+	-
E	-	+	+	+	+
Total	3	5	4	5	4

A: conditioning regimen; B: stem cell source; C: donor; D: GvHD prophylaxis regimen; E: disease status before allo-SCT; + Yes; - No

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