UPDATES ON MANAGEMENT OF REFRACTORY/ RELAPSED MULTIPLE MYELOMA AND ITS ASSOCIATED ANXIETY AND DEPRESSION: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Objectives: To study the recently published randomized control trials (RCTs) on the management of relapsed/ refractory multiple myeloma (RRMM).

Methods: We conducted a thorough search of PubMed, SCOPUS, Web of Science, and Google Scholar to find pertinent literature. Rayyan QRCI was utilized during the entire process.

Results: We included seven studies with a total of 1578 children and 953 (60.4%) were males. The follow-up duration ranged from 7.1 to 65.4 months. One study used mAb alone and reported that this line of treatment is fast, of high quality, and with a good safety profile. Another study used mAb (Daratumumab) along with an bortezomib and dexamethasone and reported that this combination showed significant efficacy advantages regarding PFS, OS, and depth of response. PFS, OS, and depth of response also were improved by using the combination of aponermin with thalidomide and Pomalidomide/ dexamethasone (EPd). Idecabtagene vicleucel (ide-cel) treatment dramatically extended PFS and enhanced response as compared to conventional regimens

Conclusion: Highly successful treatments for RRMM are assisting in the management of the condition in our patients, improving their chances of survival and preserving their quality of life. As we work to find a functional cure for myeloma patients, there is hope in sight. Novel treatments like ide-cel are demonstrating tremendous efficacy in even the most heavily treated patients, much beyond what was observed two decades ago. With myeloma becoming recognized more and more as a chronic illness, it will be critical to address issues with patient quality of life, reported outcomes, financial burdens, and unequal access to care in addition to survival and response when evaluating novel therapies.

Keywords: Multiple myeloma; Refractory; Relapsed; Management; Systematic review.

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Introduction

Excellent treatment choices are available for patients in the present era of multiple myeloma therapy, with roughly 55% of patients surviving for at least 5 years [1]. Nonetheless, myeloma is still incurable and relapses always happen at different phases of the illness, even with the use of maintenance therapy, autologous stem cell transplants, and triplet and quadruplet induction regimens. Because of the biological variability of the illness, managing relapses can be difficult and complex. Overcoming drug resistance has been a major focus of translational and clinical research over the past 20 years. Innovative treatments are quickly moving from the bench to the bedside, improving patient outcomes and lengthening lifespans.

This is an updated systematic review of the recent literature that discusses the causes and treatment lines of chronic sinusitis in children [2].

The main goal of MM treatments is to get a fully sustained response while maintaining an appropriate amount of toxicity [3]. Significant advancements in clinical results have been facilitated by the development of innovative medicines in recent times. For instance, overall survival for newly diagnosed patients has improved over the past ten years [4], with younger patients showing greater evidence of this [5].

Patients with relapsed/refractory multiple myeloma (RRMM) are a diverse group whose features vary depending on the kind and quantity of treatments received as well as the timing of relapses (early, late, or many). Principal refractory, relapsed, and relapsed and refractory are essentially the groups that are taken into consideration. Laboratory criteria, such as a ≥25% increase in the serum or urine monoclonal protein (M-protein), are used to diagnose relapsed multiple myeloma (MM), which is the disease's reappearance following a prior remission [6].

When a patient has achieved minimal response (MR) or better at some earlier stage in their treatment, or when the disease becomes unresponsive while on salvage therapy, it is referred to be RRMM [7]. Conversely, a condition that is primary refractory is one that cannot achieve an MR with any kind of treatment [8]. The choice of therapeutic approaches for elderly patients is difficult for several reasons, including their advanced age and frequently coexisting diseases [9]. This systematic review investigated the recently published randomized control trials (RCTs) on the management of RRMM.

Methodology

Study Design and Duration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in the conduct of this systematic review [10]. In April 2024, the systematic review got started.

Search strategy

To find relevant material, a comprehensive search was conducted using four key databases: PubMed, SCOPUS, Web of Science, and Google Scholar. We searched through databases that contained only English content, paying attention to the unique requirements of each. To find the relevant papers, we converted the following keywords to PubMed Mesh terms; "Multiple myeloma," "Refractory," "Relapsed," and "Management." "OR," "AND," and "NOT," three Boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Studies that discussed the recent literature that discusses the management of RRMM.
- Only RCTs
- Studies conducted in the last year (2023-2024).
- We did not include studies that discussed the treatment of RRMM with complications such as chronic kidney disease.
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

Two output verifications of the search method were conducted using Rayyan (QCRI) [11]. By using inclusion/exclusion criteria, the researchers evaluated how relevant the abstracts and titles were to the combined search results. The reviewers carefully considered every manuscript that met the inclusion requirements. The authors talked about ways to resolve conflicts. A pre-made data extraction form was used to upload the approved study. The authors extracted data on the study title, authors, study year, country, participants, age, gender, follow-up duration, treatment agents, and main outcomes. A

separate sheet was built for the risk of bias assessment.

Strategy for data synthesis

Summary tables using information from relevant studies were compiled to provide a qualitative assessment of the research's findings and components. The best technique for making use of the data from the included study articles was chosen after the data for the systematic review was gathered. Results

Search results

The systematic search produced 1190 study articles in total, of which 516 duplicates were eliminated. After 674 studies had their titles and abstracts screened, 598 were not included. After 76 reports were requested to be retrieved, 4 articles were found. After screening 72 studies for full-text assessment, 50 were rejected due to incorrect study results, 9 were rejected due to incorrect population type, 2 articles were editor's letters, and 4 were abstracts. This systematic review included seven eligible study articles. A synopsis of the procedure for choosing studies is provided in (Figure 1).

Characteristics of the included studies

(Table 1) shows the sociodemographic details of the research articles that are included. Our results included seven studies with a total of 1578 children and 953 (60.4%) were males. All of the included studies were RCTs [12-18]. Two studies were conducted in China [13, 14], two in the USA [16, 18], one in Spain [12], one in the Czech Republic [17], and one in the UK[18].

(Table 2) presents the clinical characteristics. The follow-up duration ranged from 7.1 to 65.4 months. One study used mAb alone and reported that this line of treatment is fast, of high quality, and with a good safety profile [12]. Another study used mAb (Daratumumab) [15, 14] along with an antineoplastic agent (bortezomib) and steroid (dexamethasone) and reported that this combination showed significant efficacy advantages regarding PFS, OS, and depth of response [14].

PFS, OS, and depth of response also were improved by using the combination of aponermin with thalidomide [13] and Pomalidomide/dexamethasone (EPd) [16].

Idecabtagene vicleucel (ide-cel) treatment dramatically extended PFS and enhanced response as compared to conventional regimens [17].

Single-agent belamaf at 2.5 or 3.4 mg/kg Q3W showed immediate, sustained, and clinically relevant responses with a tolerable safety profile in patients with three or more prior therapy for RRMM [18].

Discussion

This systematic review discussed updates published within the last year regarding the lines of treatment of RRMM. We first reported the use of mAb as this line of treatment was fast, of high quality, and with a good safety profile [12]. Another study used mAb (Daratumumab) [15, 14] along with an antineoplastic agent (bortezomib) and steroid (dexamethasone) and reported that this combination showed significant efficacy advantages regarding PFS, OS, and depth of response [14]. Blair, in his review also reported that Daratumumab is a useful supplement to the current therapeutic alternatives for the management of relapsed or refractory multiple myeloma, according to available evidence [19].

An era of using monoclonal antibodies to treat heavily treated MM patients began in 2015 with the fast approval of Daratumumab, an anti-CD38 IgG1 monoclonal antibody [20]. The addition of two doublet therapies-Lenalidomide with Dexamethasone and Bortezomib with Dexamethasone-was the only thing this approval covered. Isatuximab, a member of the anti-CD38 family, was initially approved in 2020 for use in RRMM in combination with dexamethasone and pomalidomide [21]. Daratumumab acts as an anti-myeloma medication through a number of mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cell-mediated cytotoxicity (ADCC) [22, 23].

Table 1. Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Age range	Gender (Males)
Ríos-Tamayo et al., 2023 [12]	RCT	Spain	With mAb (n=63) and without mAb (n=112)	64-76	96 (54.9%)
Xia et al., 2023 [13]	RCT	China	Aponermin Group (N=278) and placebo Group (N=139)	26-75	241 (57.8%)
Fu et al., 2023 [14]	RCT	China	d-vd (n=141) and vd (n=70)	28-82	116 (54.9%)
Pour et al., 2023 [15]	RCT	Czech Republic	Melflufengroup (n=27) and Daratumumabgroup (n=27)	43-83	33 (61.1%)
Dimopoulos et al., 2023 [16]	RCT	USA	EPd (n=60) and Pd (n=57)	36-81	61 (52.1%)
Rodriguez-Otero et al., 2023 [17]	RCT	UK	Ide-cel (N=254) and standard Regimen (N=132)	30-83	235 (61.4%)
Nooka et al., 2023 [18]	RCT	USA	221	NM	171 (77.4%)

*NM=Not-mentioned

Table 2. Clinical characteristics and outcomes of the included studies.

Study	Follow-up duration (months)	Treatment agent	Management
Ríos-Tamayo et al., 2023 [12]	34.9 - 65.4	Monoclonal antibodies (mAb)	When mAb is used in real-world practice to treat RRMM, the results are fast and of high quality, and the safety profile is consistent with that of randomized clinical studies.
Xia et al., 2023 [13]	17.2	Aponermin	When aponermin was coupled with thalidomide and dexamethasone, patients with RRMM who had received at least two prior regimens experienced significant improvements in PFS and OS with tolerable side effects.
Fu et al., 2023 [14]	24	Daratumumab, bortezomib, and dexamethasone (D-Vd) versus bortezomib and dexamethasone (Vd)	In terms of PFS, OS, and depth of response, D-Vd continued to show significant efficacy advantages over Vd. These outcomes were in line with the findings of the worldwide phase 3 CASTOR research.
Pour et al., 2023 [15]	7.1 - 6.6	Melflufen plus daratumumab versus daratumumab	Melflufen plus dexamethasone and daratumumab showed a safety profile similar to previously reported melflufen studies, as well as better PFS and ORR compared to daratumumab in RRMM.
Dimopoulos et al., 2023 [16]	45	EPd versus proteasome inhibitor	When compared to Pd, EPd showed a statistically significant increase in OS in individuals with RRMM.
Rodriguez-Otero et al., 2023 [17]	18.6	Idecabtagene vicleucel (ide-cel)	In patients with triple-class RRMM who had already had two to four regimens, ide-cel treatment dramatically extended PFS and enhanced response as compared to conventional regimens.
Nooka et al., 2023 [18]	12.5 - 13.8	Belamaf	Patients with three or more prior therapy for RRMM showed immediate, sustained, and clinically relevant responses with a tolerable safety profile when using single-agent belamaf at 2.5 or 3.4 mg/kg Q3W.

We also found that PFS, OS, and depth of response were improved by using the combination of aponermin with thalidomide [13] and Pomalidomide/ dexamethasone (EPd) [16]. Thalidomide was the first immuno-modulatory medication introduced in the late 1990s for relapsed refractory multiple myeloma (RRMM), which completely changed the therapy options available to patients. The FDA eventually approved Thalidomide with Dexamethasone in 2006 to treat both newly diagnosed multiple myeloma (MM) and RRMM after a phase II research involving 84 RRMM patients. Thalidomide's early success led to research into other IMiDs, the most well-known of which are Pomalidomide and Lenalidomide [24, 25].

The present study found that ide-cel treatment dramatically extended PFS and enhanced response as compared to conventional regimens [17]. Tu et al. predicted that despite ide-cel therapy's remarkable clinical success and comparatively lower toxicity, there will still be many obstacles to overcome and unanswered questions [26]. With regard to chimeric antigen receptor (CAR-T) cell therapy, there are presently two FDA-approved products: ide-cel and ciltacabtagene autoleucel (cilta-cel). For ide-cel, responses were observed in patients who had received a median of 5–9 prior lines of therapy, including an IMiD, PI, and anti-CD38 mAb [27].

Notwithstanding the seeming efficacy of these treatments, it is important to remember that patients may find it challenging to obtain these treatments outside of research trials. For example, logistical challenges pertaining to time, CAR-T cell production, and institutional adjustment restrict the use of CAR-T cell treatment in a timely way, if at all. Additionally, enrolling in a clinical trial to get novel medications usually necessitates setting up an appointment at a sizable academic medical institution, which may not be feasible for patients from underserved, rural, or minority regions. Trial administrators and pharmaceutical firms need to make an effort to spread access to these medicines to the community and rural practice context. Early partnerships with academic medical facilities, even prior to relapse, are critical in encouraging access to innovative drugs [28].

Conclusion

Highly successful treatments for RRMM are assisting in the management of the condition in our patients, improving their chances of survival and preserving their quality of life. As we work to find a functional cure for myeloma patients, there is hope in sight. Novel treatments like ide-cel are demonstrating tremendous efficacy in even the most heavily treated patients, much beyond what was observed two decades ago. With myeloma becoming recognized more and more as a chronic illness, it will be critical to address issues with patient quality of life, reported outcomes, financial burdens, and unequal access to care in addition to survival and response when evaluating novel therapies.

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