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Efficacy and toxicity profile of carfilzomib based regimens for treatment of multiple myeloma: A systematic review

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ABSTRACT

Standard induction therapy for multiple myeloma is three-drug combination based on following classes of drugs: proteasome inhibitors, immunomodulators and steroids. Despite its notable efficacy, bortezomib has side effects like peripheral neuropathy (PNP) with reported incidence of grade ≥3 PNP between 2%–23% Schlafer et al., 2017. Carfilzomib (CFZ) has high selectivity and minimal off-target adverse effects including lower rates of PNP. CFZ is already approved for treatment of relapsed and refractory multiple myeloma (RRMM) as single agent as well as in combination with lenalidomide and/or dexamethasone. Extensive literature search identified a total of 1839 articles. Twenty-six articles (n = 5980) met the inclusion criteria, 15 in newly diagnosed multiple myeloma (NDMM) and 11 in RRMM group. CFZ demonstrates comparable or even better efficacy to bortezomib with much favorable AE profile. Deep, rapid and sustainable response using KRd with safer toxicity profile supports extension of KRd therapy to frontline therapy for all risk categories of MM. High incidence of grade ≥3 HTN underscores the importance of serial BP monitoring. In RRMM, CFZ has documented efficacy with standard 20–27mg/m2 dose. Further large-scale trials are needed to study benefit-to-risk profile of 20–56 and 20–70 mg/m2 dose of CFZ vs standard 20–27 mg/m2 dose in NDMM and RRMM.

1. Introduction

Multiple Myeloma (MM) is characterized by monoclonal proliferation of plasma cells in the bone marrow. Based on cytogenetics, disease can be classified as high risk: t(14;16), t(14;20), and/or del (17p13), intermediate risk: t(4;14) and/or (1q) gain, and standard risk: trisomies, t(11;14) and/or t(6;14) (Strite et al., 2015). Consensus based treatment guidelines recommend 4 cycles of induction therapy such as bortezomib, lenalidomide and dexamethasone (VRd) followed by autologous stem cell transplantation therapy (ASCT) in transplant eligible patients with newly diagnosed multiple myeloma (NDMM) (Strite et al., 2015). Some guidelines such as mSMART recommend patients with high risk NDMM should be given carfilzomib based triple combination induction regimen. In patients with second or higher relapses, treatment depends on prior therapy, comorbidities (peripheral neuropathy, renal failure), marrow functioning as indicated by blood counts, and rapidity of relapse. Combination therapy incorporating proteasome inhibitors, immunomodulators, steroids and alkylating agents is generally recommended (Strite et al., 2015).

Over the past two decades, advancements in MM therapy have markedly improved disease outcome and overall survival (OS). According to national institute of health (NIH) cancer statistics death rates due to MM have declined on average 0.7% each year over 2005–2014 (N.C. Institute, 2018). Despite noticeable improvement in disease outcome, MM remains incurable with high rates of relapses, highlighting the unmet need for new treatment strategies. Proteasome inhibitor bortezomib was approved by the US Food and Drug Administration (FDA) for treatment of multiple myeloma in 2003 (Kane et al., 2003). Despite its notable efficacy there are serious issues of side effects such as peripheral neuropathy (PNP), which has been reported in up to 30% of patients treated with bortezomib based regimens (Mohty et al., 2010; Wang et al., 2013). Risk of PNP with bortezomib has been mitigated with subcutaneous and once weekly administration (Rosinol et al., 2012). In 2012, carfilzomib (CFZ), a novel proteasome inhibitor,

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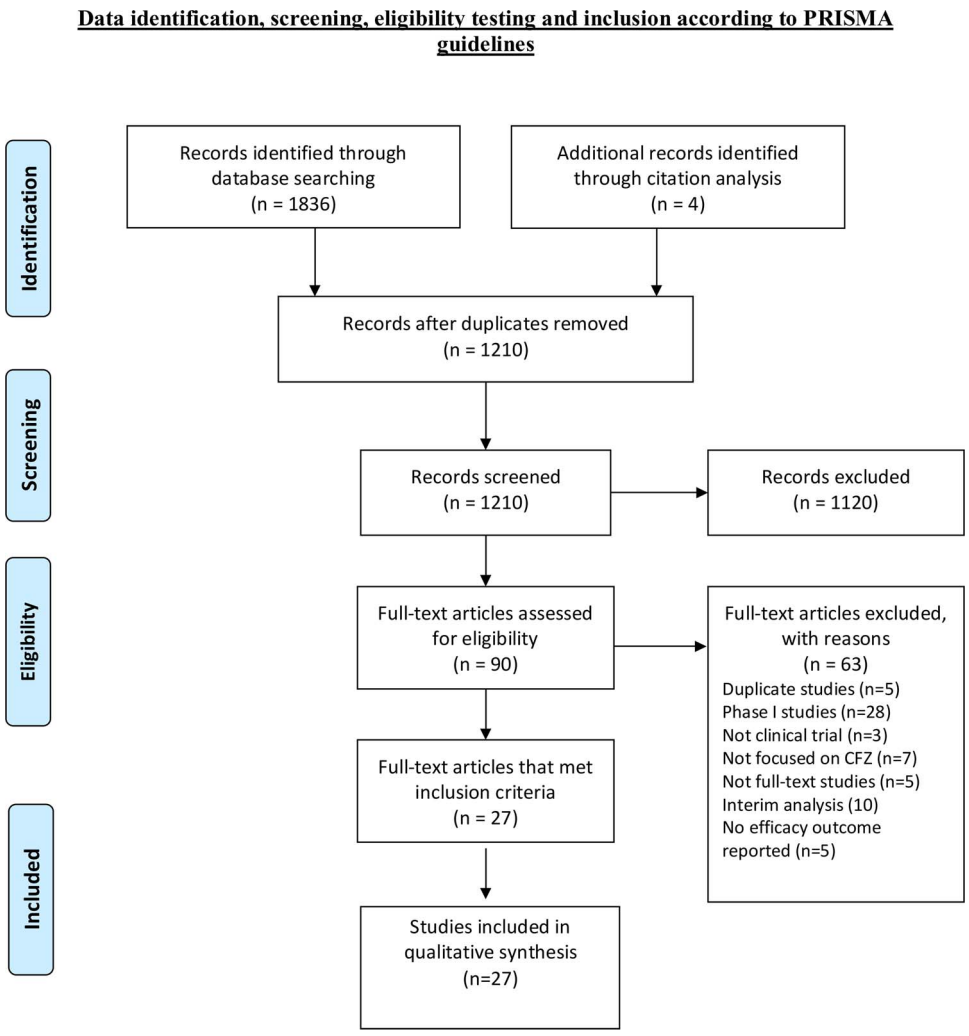

Fig. 1. Records identified through PubMed, EMBASE, Cochrane, Web of Science, Scopus, CINAHL and ClinicalTrials.gov database searches. Relevant articles from following conference proceedings were also included: the European Hematology Association, the American Society of Hematology, the American Society of Oncology and the American Society of Bone Marrow Transplantation.

was approved for treatment of relapsed and refractory multiple myeloma (RRMM) (Siegel et al., 2012a). CFZ is highly selective, irreversible epoxy-ketone molecule that targets chymotrypsin like activity of 20S proteasome leading to cellular apoptosis which is particularly beneficial in malignant cells. CFZ has minimal off target activity causing fewer side effects including lower rates of PNP (Wang et al., 2013; Moreau et al., 2015a). Further, CFZ has demonstrated activity in bortezomib resistant cell lines (Siegel et al., 2012a; Vij et al., 2012a; Jagannath et al., 2012). Since 2012, CFZ has been studied in various clinical trials. The aim of our study is to conduct comprehensive literature search for efficacy, dosing and toxicity profile of CFZ in both newly diagnosed and relapsed setting. Our secondary aim is to analyze whether CFZ treatment can be extended to the frontline setting.

2. Methods

2.1. Literature search

A comprehensive literature search was performed on 6/5/2017 in the following resources: PubMed, EMBASE, Wiley Cochrane library, Scopus, Web of Science, CINAHL, and Clinicaltrials.gov. Search results were not limited to any geographical area or language, in the case English translations were available. However, studies done only after 2007 were included. Example search strategy is provided in Appendix A. Relevant articles from following conference proceedings were also included: the European Hematology Association, the American Society of Hematology, the American Society of Oncology and the American Society of Bone Marrow Transplantation.

2.2. Eligibility criteria

Studies fulfilling the following criteria were included: (1) Phase II or III clinical trials (2) Clinical trials from last 10 years (Jan 2007 till June 2017) (3) Studies that have efficacy outcomes clearly documented and (4) Studies focusing on CFZ as primary drug therapy.

2.3. Study selection

Relevant studies were reviewed by three independent reviewers (A. M., A. L., V. K.) based on title and abstract. Potentially relevant articles were screened through full text by afore-mentioned reviewers. Any conflicts were resolved with discussion.

2.4. Data extraction and analysis

Data was extracted on pre-specified tables which included following parameters: Author, year, study design, number of patients, median age, MM staging and cytogenetics, CFZ regimen, dose, median number of cycles, and efficacy outcomes (complete response [CR], near complete response [nCR], stringent complete response [sCR], very good