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REVIEW ARTICLE

Patient-reported outcomes in relapsed/refractory multiple myeloma: a systematic review

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Abstract

Purpose We performed a systematic review to quantify the amount of evidence-based data available on patient-reported outcomes (PRO) in Relapsed/Refractory Multiple Myeloma (RRMM) patients and to examine the added value of such studies in supporting clinical decision-making.

Methods We conducted a search in PubMed/Medline and the Cochrane Library to identify studies published between January 1990 and May 2017. All studies, regardless of the design, including patients with RRMM and also evaluating PRO were considered. For each study, we collected both PRO and traditional clinical outcomes, such as survival and toxicity information, based on a predefined data extraction form.

Results After having screened 1680 records, 11 studies were identified and these included six randomized controlled trials (RCT). Overall, there were five studies focusing on proteasome inhibitors (PIs), four on immunomodulatory drugs (IMiDs), one on both PIs and IMiDs, and one on monoclonal antibodies. Considering only RCTs, it was found that primary clinical efficacy endpoints frequently favored experimental arms, while (physician-reported) toxicity data did not. However, inspection of PRO data revealed novel information that often contrasted with standard toxicity, for example, by not indicating worse quality of life outcomes or symptom severity for patients enrolled in the experimental arms.

Conclusions There is paucity of evidence-based data regarding the impact of therapies on quality of life and symptom burden of patients with RRMM. Inclusion of PRO in future studies of patients with RRMM is needed to better inform clinical decision-making.

Keywords Quality of life · Patient-reported outcomes · Relapsed · Refractory · Multiple myeloma · Adverse events

Introduction

Multiple myeloma (MM) is a neoplastic disease associated with several symptoms. These symptoms may include bone pain, fatigue, impaired renal function, and anemia, which cause an impairment of health-related quality of life (HRQOL) [1]. This term refers to a multidimensional construct which represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life [2]. However, HRQOL is only one out of a variety of other patient-reported outcomes (PRO) that are now frequently used in clinical research. PRO can be defined as any measure of patient's health, coming directly from the patient without interpretation by a physician or anyone else [3].

Achieving a durable complete response while, at the same time, an adequate level of toxicity is the primary aim of therapies for MM [4]. Development of novel treatments in recent years has contributed to major advances in clinical outcomes. For example, in the last decade, overall survival of newly diagnosed patients has increased [5], and this was more evident in younger patients [6–8]. Recent studies have demonstrated the role of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), such as bortezomib, lenalidomide, and thalidomide, in improving time to progression (TTP) and progression-free survival (PFS) on MM patients [9–11].

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Despite these major treatment advances, the disease remains broadly incurable. The only potentially curative option is allogeneic hematopoietic stem cell transplantation (allo HSCT), but this treatment is often limited to a small proportion of patients. Nevertheless, the natural history of the disease comprises sequential phases of responses, remissions and relapses, and the depth and duration of responses following each relapse usually decrease [4].

Relapsed/refractory multiple myeloma (RRMM) patients are a heterogeneous population, whose characteristics depend on the number and type of treatment used, and the type of relapse (early relapse, late relapse or multiple relapses). Basically, the following groups are considered: primary refractory, relapsed, and relapsed and refractory. Relapsed MM, that is the recurrence of the disease after a previous response, is defined based on laboratory criteria, including a ≥ 25% increase of the serum or urine monoclonal protein (M-protein) [12, 13]. Relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some previous point [14]. Primary refractory, instead, refers to disease which fails to achieve a MR with any therapy [12]. Selection of treatment strategies for these patients is challenging for a number of reasons, including the increased age and the often associated comorbid conditions [15]. Relapsed/refractory myeloma patients are also more symptomatic, more vulnerable to adverse events (AEs) and, therefore, more likely to incur a dose reduction or early discontinuation of therapy. Indeed, AEs and treatment discontinuation are associated with poorer outcomes and greater risk of death [16]. For example, patients who become refractory to PIs and IMiDs have poor survival, reporting an average life expectancy of 9 months from the time of failing first line PIs and IMiDs [17]. Balancing expected efficacy of therapy against potential toxicities and impact on patients' HRQOL is therefore critical in this patient population. Also, the benefits of early palliative care should not be underestimated [18].

The majority of studies that have assessed HRQOL in MM patients have mainly focused on newly diagnosed patients enrolled in randomized controlled trials (RCT) [19] or have addressed specific methodological issues in the design and the reporting of HRQOL outcomes [20]. For example, Nielsen et al. have recently published a review looking into changes in EORTC QLQ-C30 [21] scores, in MM longitudinal studies [22].

Therefore, we performed a systematic review with the objective of quantifying the amount of evidence-based data available on HRQOL in RRMM patients published since 1990. In addition, we also examined the possible added value of RRMM patients' perspectives in supporting clinical decision-making.

Materials and methods

Search strategy for identification of studies

We conducted a systematic literature search in PubMed/Medline and in Cochrane Library to identify studies published between January 1990 and May 2017. Additional publications were identified by hand-searching reference lists of relevant articles. We have also consulted with content experts in MM research to possibly identify additional eligible articles that we might have missed through electronic search. The starting point of the research was 1990 in order to best capture the studies focusing on new drug therapies for RRMM. The key search strategy used to retrieve eligible articles is reported in Appendix 1. The search strategy included all varieties of studies, excluding reviews and case reports. Only English language articles were considered and abstracts of identified articles were screened for inclusion. If a selected study had multiple publications, we considered them all in the data extraction process in order to maximize quality of information in our review.

Selection criteria

Types of participants

Studies with adult patients diagnosed with primary refractory, relapsed, and relapsed and refractory multiple myeloma were included. Studies focusing on newly diagnosed patients were excluded. No restriction was applied with regard to the number of patients enrolled.

Types of intervention

All studies conducted in RRMM patients receiving any kind of treatment were eligible for inclusion.

Types of studies

We included all type of studies (regardless of the design) conducted in RRMM patients incorporating a PRO measure. Studies including a heterogeneous sample of cancer sites were excluded. We excluded studies including both RRMM and newly diagnosed MM patients, in which the results were analyzed together [23, 24] and studies where it was not specified that the population was composed by RRMM [25, 26], despite the patients receiving different lines of treatment, due to the difficulty to attribute the findings to RRMM population. Conference abstracts and case reports were excluded due to their lack of necessary information to assess quality of PRO reporting.

Data extraction and type of information considered

Before beginning the literature search, a predefined coding schema for data extraction was developed. The data extraction form included various information on (1) basic trial demographics (i.e., year, journal, age of patients, overall study sample size, study location); (2) clinical characteristics (i.e., type of therapy, prior treatments, prior lines of therapy); (3) PRO design characteristics (i.e., patients included in the PRO analysis, PRO instrument used and timing of HRQOL assessment); (4) summary of findings (i.e., statistically and clinically meaningful PRO outcomes, clinical endpoints) and treatment recommendations by authors. This latter was based on how authors themselves summarized their findings and what treatments they recommended, based on traditional clinical and PRO outcomes. PRO information extracted was grouped into predefined categories depending on whether or not statistically or clinically meaningful differences between treatment arms (if more than one) or from baseline (if single arm trial) at any time point were found. If the difference was found only in a single scale, PRO outcomes were categorized as "symptoms only," "functional scale only," or "Global Health Status/QoL scale only," depending on the single item or scale where the difference was registered. If the difference was found in more than a scale, the outcomes were categorized as "mixed outcome," otherwise, if no difference were found, we categorized it as "study equivalence." Each study selected was evaluated independently by two reviewers (FS and FE), and, when disagreements occurred with regard to the extracted information, the reviewers revisited the paper/s to reconcile any differences until consensus was achieved.

Results

The literature search yielded 1680 records, published until May 2017, that were screened for eligibility. We retrieved a total of 18 papers, published from June 2003 to March 2017, comprising of 11 studies. Figure 1 details the search strategy and the selection process of the articles included in this review, which were complied with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [27].

Overview of patient characteristics and study design

The overall number of patients enrolled was 4035, ranging from a sample size of 32 to 792 (63.6% of the studies enrolled more than 200 patients). Six studies were RCT and the median age of patients enrolled in all studies identified ranged from 30 to 91 years. All the studies included were multicenter and ten of them (90.9%) were international studies. Two of the most recent studies investigated the role of carfilzomib [28, 29] and pomalidomide [30–32], that is the most recently approved IMiDs for the treatment of myeloma patients [33]. Two studies (18.2%) focused on bortezomib therapy [34–39] two on thalidomide [40, 41], one (9.1%) on the most recently Food and Drug Administration (FDA) approved PIs, ixazomib [42], one on elotuzumab [43], one on lenalidomide [44], one both on lenalidomide and bortezomib [45], and one on ALCAR [46]. The number of prior lines of therapy ranged from one to 17. Full details are reported in Table 1.

Overview of PRO instruments used

In all studies, except one [45], PRO were included as secondary endpoints. The EORTC QLQ-C30, used alone or in conjunction with its specific myeloma module [47], was the most frequently used instrument, being employed in ten studies (90.9%). The FACT/GOG-Ntx [48] was used in three studies (27.3%) and the FACIT-Fatigue scale [49] was used in two studies (18.2%).

In one study [30–32], authors employed five of the 15 EORTC QLQ-C30 scales (Global Health Status/QoL scale, Physical Functioning, Emotional Functioning, Fatigue and Pain), two of the four EORTC QLQ-MY20 scales (Disease Symptoms and Side effects of treatment) and EQ-5D Health Utility Index. Stewart AK et al. [28, 29] used six EORTC QLQ-C30 scales (Global Health Status scale/QoL scale, fatigue, pain, nausea/vomiting, physical functioning, and role functioning) and two EORTC QLQ-MY20 scales (disease symptoms and side effects of treatment), whereas remaining studies used all the domains of the instruments employed. Details are reported in Table 2.

Proteasome inhibitors and PRO

Six studies (54.5%) investigated the use of PIs (ixazomib, carfilzomib, and bortezomib) and their impact on HRQOL and overall survival (OS). In one study [37–39], bortezomib was associated with a median OS of 16 months (data on statistical significance are not reported), while it induced clinically meaningful improvements in 10 PRO scales. In another study, bortezomib was compared with dexamethasone [34–36] and it demonstrated improved survival, as OS for this group was 29.8 compared with 23.7 of dexamethasone. Also, this study showed that bortezomib was associated with higher AEs but better HRQOL, since ten scales resulted in better outcomes with respect to the dexamethasone group. Leleu et al. [45] observed that patients who completed the 6 month treatment with bortezomib worsened only in the Global Health Status/QoL scale, compared with those who discontinued the therapy prior to 6 months, who declined on eight scales. In Callander et al. [46], the addition of ALCAR to bortezomib, doxorubicin and dexamethasone did not demonstrate statistical significant differences in OS and PRO outcomes. In Moreau et al. [42], ixazomib was associated with

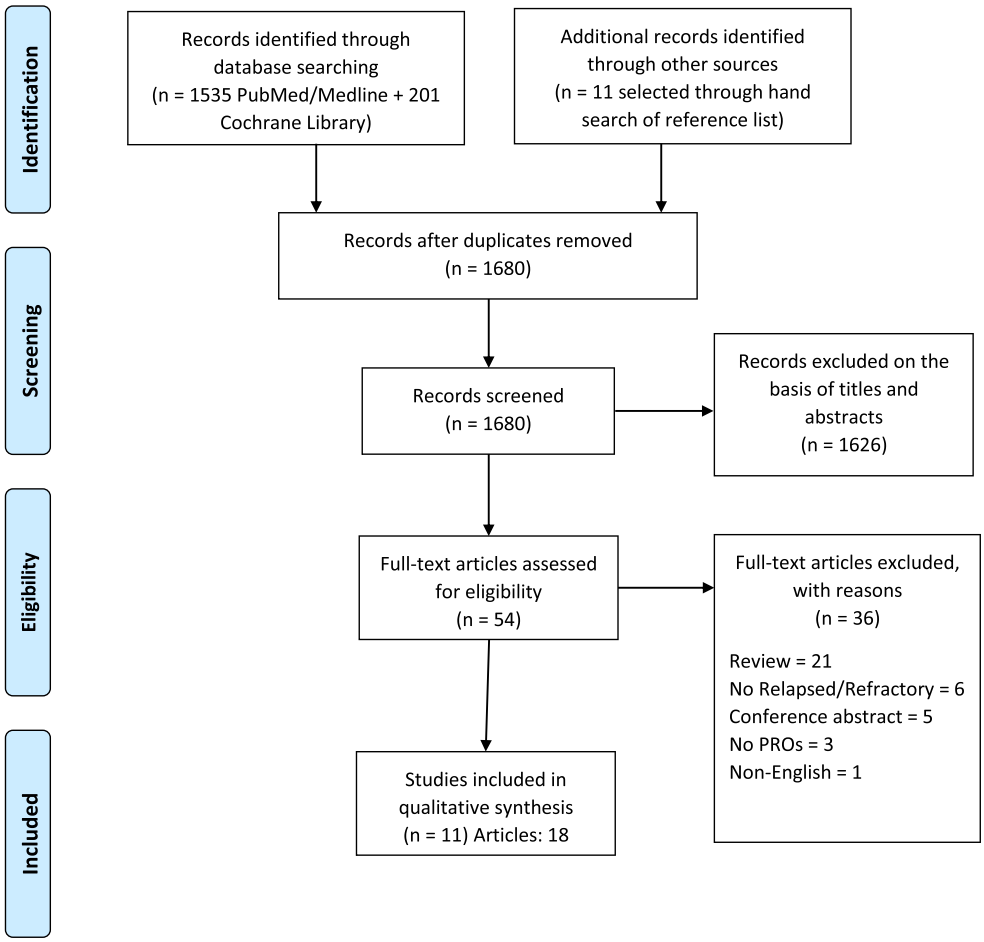

Fig. 1 Schematic breakdown of literature search results of RRMM studies

longer progression-free survival (PFS), but AEs (any grades), including constipation, nausea and vomiting were generally reported at higher rates with this drug. PRO outcomes were similar between groups, with a trend for less fatigue and better physical and emotional functioning in the ixazomib regimen. In Stewart et al. [28, 29], median overall survival was not reached in either group, but resulted a trend in favor of carfilzomib group. Any grade non-hematologic AEs were reported at higher rates in the experimental arm. The same group reported better clinically meaningful outcomes in the EORTC QLQ-C30 Global Health Status/QoL scale, reaching minimal important differences (MID) at cycle 12 and approaching it at cycle 18 of treatment.

Immunomodulatory drugs and PRO

Five studies (45.5%) investigated the impact of IMiDs (Lenalidomide, Thalidomide and Pomalidomide) on HRQOL and OS. Thalidomide, in Waage et al. [41], was associated with a median overall survival of 12 months (statistical significance is not reported) and with stable HRQOL scores, except for clinically significant improvement of pain and increase of constipation. The same therapy, assessed in a RCT by Hjort et al. [40], was associated with an OS of 22.8 months, compared with 19 months of the control group (bortezomib), but no data about statistical significance was reported. In the PRO analysis, no clinically meaningful differences in favor of thalidomide were found. Lenalidomide was investigated in Alegre et al. [44], where median overall survival was not reached, while clinically meaningful improvements were only found in the EORTC QLQ-MY20 "Future perspective" scale. In Leleu et al. [45], patients in lenalidomide group maintained substantially their HRQOL, with only a clinically meaningful deterioration on diarrhea. Better results were reached with pomalidomide [30–32]: OS was 12.7 months comparing with 8.1 months of the control group; statistical and clinically significant differences were found in most scales of the PRO instruments used.

Monoclonal antibodies and PRO

One study (9.1%) evaluated the efficacy and safety of elotuzumab, a humanized monoclonal antibody anti-SLAMF7, on RRMM patients [43]. This agent, in combination with lenalidomide and dexamethasone, improved PFS and overall response rate (ORR), compared with lenalidomide and dexamethasone alone (19.4 vs. 14.9 months and 79 vs. 66%, respectively). However, AEs (any grades), including

Table 1 General study characteristics

Study	Study design	Age[a]	Type of intervention	Overall study sample size	Prior lines[b]	Prior treatments	Clinical endpoints[c]
Leleu X et al., Blood Cancer J 2017;7(3):e543	Prospective, multicentre, non--interventional, longitudinal study	Bort: 69 (62–74) Len: 72 (66–77)	Patients received second or third line lenalidomide or bortezomib treatment	258 (96 Bort, 162 Len)	(1–2)	Not reported	No clinical endpoints
Moreau P et al., N Engl J Med. 2016;374(17):162-1–34	RCT	Ixazomib: 66 (38–91) Placebo: 66 (30–89)	Patients were randomly assigned, in a 1:1 ratio, to receive, in 28-day cycles, either 4 mg of oral ixazomib or matching placebo on days 1, 8, and 15; in addition, all patients received 25 mg of oral lenalidomide on days 1 through 21 (10 mg for patients with a creatinine clearance of ≤ 60 or ≤ 50 ml per minute per 1.73 m2, with the cutoff point determined according to the local prescribing information) and 40 mg of oral dexamethasone on days 1, 8, 15, and 22	722 (360 Ixazomib, 362 Placebo)	(1–3)	Ixazomib: Bort (69%), Thal (44%), Len (12%), CFZ (< 1) Placebo: Bort (69%), Thal (47%), Len (12%), CFZ (1%)	Primary end point: PFS: Ixazomib (20.6) vs. Placebo (14.7) HR 0.74 (95% CI 0.59–0.94) $p = 0.01$ Secondary end points: OR: Ixazomib (78.3) vs. Placebo (71.5) $p = 0.04$; OS: median not reached; ≥ 3 grade AEs: Ixazomib (74) vs. Placebo (69%)
Lonial S et al., N Eng J Med. 2015; 373(7):621–31	RCT	Elotuzumab: 67 (37–88) Control: 66 (38–91)	10 mg of intravenous elotuzumab per kilogram of body weight on days 1, 8, 15, and 22 during the first two cycles and then on days 1 and 15 starting with the third cycle. They also received oral lenalidomide (at a dose of 25 mg per day) on days 1 through 21 of each cycle. Dexamethasone was administered orally at a dose of 40 mg during the week without elotuzumab and intravenously at a dose of 8 mg plus 28 mg orally on the day of elotuzumab administration	646 (321 Elotuzum-ab, 325 Control)	2 (1–4)	Elotuzumab: Bort (68%), Melphalan (69%), Thal (48%), Len (5%). Control: Bort (71%), Melphalan (61%), Thal (48%), Len (6%)	Primary end point: PFS: Elotuzumab (19.4) vs. Control (14.9) HR 0.70 (95% CI 0.57–0.85) $p < 0.001$; OR: Elotuzumab (79) vs. Control (66) $p < 0.001$ Secondary end points: OS: follow-up data are not yet mature enough; serious AEs: Elotuzumab (65) vs. Control (57)*

Table 1 (continued)

Study	Study design	Age[a]	Type of intervention	Overall study sample size	Prior lines[b]	Prior treatments	Clinical endpoints[c]
Stewart AK et al., J Clin Oncol. 2016; 34:3921–3930 Stewart AK et al., N Engl J Med. 2015; 372(2):142–52	RCT	CFZ: 64 (38–87) Control: 65 (31–91)	18 cycles of 28 days: CFZ was administered on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg per square meter on days 1 and 2 of cycle 1; target dose, 27 mg per square meter thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 during cycles 13 through 18, after which CFZ was discontinued. Len (25 mg) was given on days 1 through 21. Dex (40 mg) was administered on days 1, 8, 15, and 22	792 (396 CFZ, 396 Control)	2 (1–3)	Bort: 65,8% Len: 19,8%	Primary end point: PFS: CFZ (26.3) vs. Control (17.6) HR 0.69 (95% CI 0.57–0.83) $p = 0.0001$ Secondary end points: OR: CFZ (87.1) vs. Control (66.7) $p < 0.001$; OS: median not reached in either group with trend in favor of CFZ; ≥ 3 grade AEs: CFZ (83.7) vs. Control (80.7)*
Weisel K et al., Clin Lymphoma Myeloma Leuk. 2015; 15(9):519–30; Song KW et al., Haematologica. 2015; 100(2):e63–7 San Miguel J et al.; Lancet Oncol. 2013; 14(11):1055–66;	RCT	Pom: 64 (35–84) HiDex: 65 (35–87)	Patients were randomized 2:1 to receive 28-day cycles of Pom 4 mg on days 1 to 21 + Low Dex 40 mg (20 mg for patients aged > 75 years) weekly or High Dex 40 mg (20 mg for patients aged > 75 years) on days 1 to 4, 9 to 12, and 17 to 20	455 (302 Pom, 153 High Dex)	Pom: 5 (2–14)H-igh Dex: 5 (2–17)	Pom: Dex (98%), Thal (57%), ASCT (71%), Len (100%), Bort (100%). High Dex: Dex (99%), Thal (61%), ASCT (69%), Len (100%), Bort (100%).	Primary end point: PFS: Pom+Low Dex (4.0) vs. High Dex (1.9) HR 0.48 (95% CI 0.39–0.60) $p < 0.0001$ Secondary end points: OS: Pom+Low Dex (12.7) vs. High Dex (8.1) HR 0.74 (95% CI 0.56–0.97) $p < 0.0285$; TTP: Pom+ Low Dex (4.7) vs. High Dex (2.1) HR 0.46 (95% CI 0.36–0.59) $p < 0.0001$; OR (CR+VGPR+PR): Pom+Low Dex (31) vs. High Dex (10) $p < 0.0001$; 3–4 grade AEs: Neutr. Pom+Low Dex (48) vs. High Dex (16); Infections: Pom+Low Dex (30) vs. High Dex (24)*
Callander N et al., Cancer Chemother Pharmacol. 2014; 74:875–882	Non-randomized phase II trial	64,5 (39–88)	In the first half of the study patients received Bort (B) 1.3 mg/m2 on day 1, 4, 8 and 11 intravenously, doxo-rubicin (D) 15 mg/m2 on days 1 and 8 intravenously and Dex (D) 20 mg by mouth on days 1, 4, 8 and 11 for up to 8 cycles without ALCAR (A). Patients ac-crued to the second part of the study received BDD plus ALCAR (1.5 g by mouth twice daily)	32 (19 BDD group and 13 BDD plus ALCAR (BDD-A) group)	5 (1–8)	Bort: 59%	CR+PR: BBD (53) vs. BBD-A (54)* OS: BBD (22.9) vs. BBD-A (28.3) p = not significant ≥3 grade PN: BBD (32) vs. BBD-A (15) p = not significant

Table 1 (continued)

Study	Study design	Age[a]	Type of intervention	Overall study sample size	Prior lines[b]	Prior treatments	Clinical endpoints[c]
Alegre A et al., Leuk Lymphoma. 2012; 53(9):1714–21	Open-label, multicenter single-arm trial	62 (42–84)	Patients received Len (25 mg/day, day 1–21)+ high-dose Dex (40 mg/day, day 1–4, 9–12 and 17–20) every 28-day cycle for Cycles 1–4. Starting at Cycle 5, Dex was reduced to 40 mg/day for days 1–4 every 28 cycle	63	Not reported	Alkilating agents (81%), Vinca alkaloids (75%), Anthracycline (68%), SCT (68%), Bort (59%)	Primary end point: AEs: ≥ 1 treatment-related 3–4 grade AEs (73), Neutropenia (51), Thrombocytopenia (14) Secondary end points: PFS: 13.3; TTP: 13.3; OR: 78; CR: 21; OS: median not reached
Hjorth M et al., Eur J Haematol. 2012; 88(6):485–9	RCT	Thal-Dex: 71 (38–85) Bort-Dex: 71 (50–84)	Patients were randomized 1:1. In the Thal-Dex group, thal was given at a dose of 50 mg once daily initially, escalated by 50 mg every 3 wk to a maximum of 200 mg daily, unless sufficient response was achieved by a lower dose. Dex dose was 40 mg on days 1–4, repeated every third week. In the Bort-Dex group, Bort was given with 1.3 mg/m2 intravenously on days 1, 4, 8, and 11 of a 3-wk cycle. Dex dose was 20 mg on days 1–2, 4–5, 8–9, and 11–12. In both groups, treatment was continued until the achievement of best response followed by 1–2 additional 3-wk treatment cycles, followed by a treatment pause	131 (67 Thal-Dex group, 64 Bort-Dex group)	Not reported	High-dose Melphalan: Thal-Dex group (49%), Bort-Dex group (52%)	Primary end point: PFS: Thal-Dex 9.0 (95% CI 4.3–10-4) vs. Bort-Dex 7.2 (95% CI 3.9–11.5)* Secondary end points: PR+VGPR: Thal-Dex (55) vs. Bort-Dex (63) p = not significant; VGPR: Thal-Dex (13) vs. Bort-Dex (36) $p < 0.01$; OS: Thal-Dex 22.8 (95% CI 16.0–34.7) vs. Bort-Dex 19.0 (95% CI 15.9–35.6)*; Toxicity: SMN 3–4 grade Thal-Dex (6) vs. Bort-Dex (12); NP 2–4 grade Thal-Dex (5) vs. Bort-Dex (21)*
Lee SJ et al., Br J Haematol. 2008; 143(4):511–9 Richardson PG et al., N Engl J Med 2005;352:2487–98 Richardson PG et al., Blood. 2007; 110(10):3557–60	RCT	Bort: 62 (48–74) Dex: 61 (47–73)	Bort group received 1,3 mg/m2 on days 1, 4, 8, and 11 for eight 3-week cycles, followed by three 5-week maintenance cycles with Bort 1,3 mg/m2 on days 1, 8, 15, and 22. Dex group received 40 mg/d on days 1 to 4, 9 to 12, and 17 to 20 for four 5-week cycles, and on days 1 to 4 only for five 4--week cycles	669	2	Bort: Corticosteroids (98%), Alkilating agents (91%), Anthracyclines (77%). Thal (48%), Vinca alkaloids (75%), SCT (67%) Dex: Corticosteroids (99%), Alkilating agents (92%), Anthracyclines (76%). Thal (50%), Vinca alkaloids (72%), SCT (68%)	Primary end point: TTP: Bort (6.22) vs. Dex (3.49) HR 0.55 $p < 0.001$ Secondary end points: CR+PR: Bort (38) vs. Dex (18) $p < 0.001$; OS (extended follow-up): Bort (29.8) vs. Dex (23.7) HR = 0.77 $p = 0.027$; 3–4 grade AEs: Bort (75) vs. Dex (60)*

Table 1 (continued)

Study	Study design	Age[a]	Type of intervention	Overall study sample size	Prior lines[b]	Prior treatments	Clinical endpoints[c]
Dubois D. et al., J Clin Oncol 2006; 24:976–982 Viala M et al., J Clin Epidemiol. 2007; 60(7):670–679 Richardson PG et al., N Engl J Med 2003;348:2609–17	Multicenter, open-label, non-randomized, phase II trial	60[d] (34–84)	Bort 1.3 mg/m2 in up to eight treatment cycles in patients with refractory MM after at least two previous treatments. During each treatment cycle, Bort was administered twice per week for 2 weeks (days 1, 4, 8, and 11), with each treatment cycle being 21 days. Maximum duration of treatment was eight cycles	202	6 (2–15)	Corticosteroids (100%), Alkilating agent (92%), anthracycline (81%), Thal (83%), SCT (64%)	Primary end points: OR (CR + PR + MR): 35* Secondary end points: TTP: 7 $p = 0.01$; OS: 16*; 4 grade AEs: 14*
Waage A et al., Br J Haematol. 2004; 125(2):149–55	Non-randomized phase II trial	63 (31–78)	Thal was given as a single agent at a dose of 100 mg twice daily, which was escalated to 400 mg twice daily over 5 weeks. The dose was maintained for 6 months, after that time a decision whether to continue the medication or not was made by investigator. Patients who did not respond to Thal within 3 months were allowed to start alternative medication	65	> 2 (32)[e]	PBSC: 41% Other: 83%	CR+PR: 20* OS: 12*

AEs adverse events; *ALCAR* Acetyl-L-carnitine; *APEX* Assessment of Proteasome Inhibition for Extending Remissions; *ASCT* autologous stem cell transplantation; *ASPIRE* CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of PatIents with Relapsed Multiple MyEloma; *BDD* bortezomib, doxorubicin, dexamethasone; *Bort* bortezomib; *CR* complete response; *CFZ* carfilzomib; *Dex* dexamethasone; *EORTC QLQ-C30* European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; *GHS* Global Health Status/QoL scale; *HiDex* high-dose dexamethasone; *HR* hazard ratio; *HRQoL* health-related quality of life; *HT* haematological toxicity; *Len* lenalidomide; *MM* multiple myeloma; *MR* minimal response; *Neutr.* neutropenia; *NP* neuropathic pain; *OR* overall response; *OS* overall survival; *PBSC* high-dose melphalan with peripheral blood stem cell; *PFS* progression-free survival; *PN* peripheral neuropathy; *Pom* pomalidomide, *PR* partial response; *PROs* patient-reported outcomes; *QoL* quality of life; *RRMM* relapsed/refractory multiple myeloma; *RCT* randomized controlled trial; *SCT* stem cell transplantation; *SMN* sensor or motor neuropathy; *SUMMIT* Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; *Thal* thalidomide; *TTP* time to progression; *VGPR* very good partial response

[a] Median (range)

[b] Median (range)

[c] PFS, OS, TTP data are median months; SMN and NP data are N. of patients; others data are %

[d] Mean

[e] Number (percentage)

*Statistical significance not reported

fatigue, diarrhea and constipation were generally reported at higher rates with this drug. In the PRO analysis, there were no significant differences between groups in pain and in health-related quality of life measures.

Overview of treatment recommendations

Recommendations by authors are summarized in Table 2. Authors of TOURMALINE-MM1 study [42], on the basis of benefits reported on PFS and a maintained HRQOL, recommended the addition of ixazomib to the doublet regimen of lenalidomide-dexamethasone, for RRMM patients. Authors of SUMMIT study [37–39] reported that bortezomib induced, in RRMM patients, clinically significant responses, and that the most common AEs (e.g., gastrointestinal symptoms, fatigue, thrombocytopenia) were manageables. In addition, the study demonstrated the complementary value of PRO assessments. Authors of APEX study [34–36] demonstrated that bortezomib therapy was superior to high-dose of dexamethasone, for RRMM patients who received up to three previous therapies other than bortezomib. Furthermore, consistent with clinical outcomes, this therapy was associated with better HRQOL outcomes. Callander et al. [46] did not recommend the addition of ALCAR to bortezomib, doxorubicin, and dexamethasone, as it did not eliminate treatment-related peripheral neuropathy. Stewart et al. [28, 29] stated that the addition of carfilzomib to lenalidomide and dexamethasone had a favorable risk-benefit profile, leading to improvements in PFS, HRQOL, and response rates, despite reporting higher numbers of common AEs. The authors highlighted the importance that the improvement of the efficacy was not at the cost of an impairment of HRQOL.

Regarding IMiDs studies, Waage et al. [41] affirmed that no relationship between thalidomide and effects after 12 weeks was found, although they did not exclude that such a relationship exists. According to Hjorth et al. [40], thalidomide, in combination with dexamethasone, seemed to have an efficacy compared with bortezomib plus dexamethasone in melphalan refractory myeloma patients; nonetheless, the statistical strength of the study was not optimal. However, authors recommended bortezomib for patients with advanced disease and in need of a rapid response. According to Alegre et al. [44], the study demonstrated that lenalidomide was effective and generally tolerated by RRMM patients. Regarding PRO analysis, no changes in median HRQOL scores were seen, except in "Future perspective" scale. For the authors, this suggested that, overall, the therapy did not negatively impact patient's HRQOL and that, for an appreciable percentage of them, it produced clinically meaningful improvements. Finally, authors of MM-003 trial [30–32] demonstrated that pomalidomide could be considered a new treatment option for patients with RRMM who failed with bortezomib and lenalidomide therapy.

Leleu et al. [45] stated that continuous treatment with lenalidome or bortezomib, despite being associated with adverse events, did not deteriorate patients' HRQOL.

Authors of ELOQUENT-2 study [43] elaborated their conclusions only on the base of primary clinical endpoints, highlighting the role of elotuzumab on improving PFS and ORR, but no mention was made to PRO.

Discussion

In this systematic review, we have quantified the amount of evidence-based data on the impact of salvage therapies on HRQOL and other type of PRO in patients with RRMM. Although we searched for studies published up to May 2017, we found only eleven studies. This dearth of information is striking considering the potential value that PRO information could provide to facilitate clinical decision-making in this vulnerable population.

Past reviews have focused on methodological quality of HRQOL assessments [20] by investigating methods of data collection, analysis, and reporting [19] or included studies both on newly diagnosed patients and RRMM [22]. In this work, we focused on the added value of PRO assessment in supporting clinical decision-making for RRMM therapies. We found that in most cases PRO assessment was an important factor, as PRO added novel information compared to physician-reported AEs. In this review, the studies focusing on PIs were associated with better OS and with clinical meaningful differences in several PRO scales. Carfilzomib reported improved results on Global Health Status/QoL scale [28, 29]; the use of bortezomib was associated with improvements both on Global Health Status/QoL scale and on symptoms and functional scales, in particular physical, role, emotional, and social functioning [34–39]. The HRQOL was maintained by the use of ixazomib [42] and a trend for less fatigue, emotional and physical functioning was found. In the studies about IMiDs, fewer PRO scales reached clinical meaningful differences and data about the statistical significance were frequently not reported. Pomalidomide was associated with better HRQOL on symptoms and functional scales, a result that was concordant with better clinical outcomes reached from patients treated with this therapy [30–32]. Lenalidomide was associated with meaningful improvements in the EORTC QLQ-MY20 "Future perspective scale" [44], while thalidomide was associated with an improvement and a worsening in, respectively, EORTC QLQ-C30 pain and constipation scales [41]. In the only study about monoclonal antibodies [43], elotuzumab did not improve HRQOL, but better results were found for PFS. Inspection of the reported AEs showed that, in most cases, all grades AEs reported in the experimental group were higher

Table 2 PRO characteristics

Authors	Patients included in the PRO analysis[a]	Timing of PRO assessment	PRO instrument/s	Statistically and clinically meaningful PRO outcomes[b]	Treatment recommendations by the authors
Leleu X et al.	258	At baseline, 3 and 6 months following treatment initiation and/or study discontinuation	EORTC QLQ-C30 EORTC QLQ-MY20 EORTC QLQ-CIPN20	Mixed outcome: For patients still on treatment at study completion (month 6), only the EORTC QLQ-C30 domains of diarrhea and Global Health Status/QoL had worsened in the lenalidomide and bortezomib cohorts, respectively. A clinically meaningful deterioration in HRQoL was more often observed for patients who discontinued the study prior to 6 months in the bortezomib cohort (Global Health Status/QoL, Role functioning, Social functioning, Fatigue, dyspnoea, diarrhea, Motor scale and Sensory scale) than in the lenalidomide cohort (Motor scale)	This study has enabled us to observe, in a real-world setting, the impact that continuous treatment over a 6-month period had on the patients' HRQoL scores and showed that they did not substantially deteriorate, despite receiving treatment with associated adverse events that could have potentially impacted patient's well-being. Importantly, some differences in HRQoL deterioration were observed between bortezomib and lenalidomide at the time of discontinuation of treatment
Moreau P et al.	714	Every 2 cycles until disease progression	EORTC QLQ-C30 EORTC QLQ-MY20	Study equivalence	The addition of ixazomib to a regimen of lenalidomide–dexamethasone led to significantly longer PFS in RRMM patients, with limited additional toxic effects; in consideration of its adverse-event profile and efficacy, this all-oral regimen provides an additional therapeutic option for RRMM patients
Lonial S et al.	646	At baseline, on day 1 of each cycle, and at the end of treatment or withdrawal from the study	EORTC QLQ-C30 EORTC QLQ-MY20 BPI-SF	Study equivalence	Patients with relapsed or refractory multiple myeloma who received a combination of elotuzumab, lenalidomide, and dexamethasone had a significant relative reduction of 30% in the risk of disease progression or death
Stewart AK et al. 2016 and 2015	696	On day 1 of cycles 1 (baseline), 3, 6, 12, and 18; and at the post-treatment visit (30 days after last treatment administration)	EORTC QLQ-C30 EORTC QLQ-MY20	Global health status/QoL scale only: Using a restricted maximum likelihood-based mixed model for repeated measurements analysis under the assumption of missing at random, CFZ group reported improved GHS status compared with the control group over 18 cycles of treatment. The MID on the GHS scale is 5.0 points, which was met at cycle 12 (5.6) and approached at cycle 18 (4.8)	In RRMM patients, the addition of CFZ to Len and Dex resulted in significantly improved PFS at the interim analysis and had a favorable risk-benefit profile CFZ, lenalidomide and dexamethasone (KRd) improves GHS without negatively affecting patient-reported symptoms when compared with control group. These data further support the benefit of CFZ in RRMM patients
Weisel K et al.; Song KW et al.;	433: 289 Pom+Low Dex and 144 High Dex	At baseline, on day 1 of each cycle (10 cycles totally) and at treatment discontinuation	EORTC QLQ-C30 EORTC QLQ-MY20 EQ-5D	Mixed outcome: Clinically meaningful improvements in HRQoL as determined by MIDs, regression analyses, and best response analyses were observed	Pom+Low Dex could be considered a new treatment option for patients with advanced RRMM in whom treatment with Bort and Len has been unsuccessful

Table 2 (continued)

Authors	Patients included in the PRO analysis[a]	Timing of PRO assessment	PRO instrument/s	Statistically and clinically meaningful PRO outcomes[b]	Treatment recommendations by the authors
San Miguel J et al.				more frequently in patients receiving Pom+ Low Dex. Significant differences in MID-based responses were observed in Physical Functioning, Emotional Functioning, Health Utility, and Fatigue scores. A statistically significant odds ratio was shown for EORTC QLQ-C30 domains of Physical Functioning, Emotional Functioning and Fatigue. Significant differences in the MID best responses were seen in each of the 5 EORTC QLQ-C30 domains and in EQ-5D Health Utility	
Callander N et al.	13 (BDD-A group)	At the time of enrollment and prior to each odd cycle (8 cycles)	FACT-GOG-NTX FACIT-Fatigue	Study equivalence	The study suggests that the addition of ALCAR did not eliminate treatment-related PN
Alegre A et al.	> 79% completed HRQoL questionnaires at baseline. 42 patients completed the questionnaires at 24 weeks	HRQoL assessments were conducted at baseline and after 24 weeks of treatment	EORTC QLQ-C30 EORTC QLQ-MY20	Functional scale only: Clinical meaningful improvements (≥ 5 points change from baseline) was only found in the "future perspective" domain of the EORTC QLQ-MY20 (11.1 points)[c]	No change in median QoL scores was seen, except in the "future perspective" category. This suggests that, overall, Len+Dex salvage therapy does not negatively impact patient QoL and, for an appreciable percentage of patients, demonstrates clinically meaningful improvements. The findings of this study support previous phase III data showing that Len+Dex is effective and generally well tolerated in patients with RRMM
Hjorth M et al.	EORTC QLQ-C30 was completed by (96) of patients still alive at 6 wk., (90) at 12 wk, and (76) at 6 months	Patients completed the questionnaires before randomization, before start of treatment, and later mailed to the patients after 6, 12 wk., 6 months, and thereafter every 6 months until the end of the study	EORTC QLQ-C30	Symptoms only: Among EORTC QLQ-C30 Insomnia scale, Bort-Dex group reported higher scores reaching statistical significance at 6 and 12 week. The score increased by 14 points from the time of randomization and the difference amounted at 20 points at 12 wk. (differences or changes of 10 or more points were regarded as clinically significant)	Thal, in combination with Dex, seems to have an efficacy comparable with that of Bort+Dex in melphalan refractory myeloma. For the majority of patients, in the absence of differences in efficacy, the choice of initial treatment should be based on the differences in toxicity, QoL aspects, and other patient related factors. For a patient with advanced disease with threatening complications, when a rapid response is desirable, Bort may be the preferred drug. For both drugs, measures should be taken to prevent evitable toxicity
Lee SJ et al.; Richardson PG et al.	598 for the EORTC QLQ-C30 analysis. 606 for the	At baseline and weeks 6, 12, 18, 24, 30, 36, and 42	EORTC QLQ-C30 FACT/GOG-NTX	Mixed outcome: Different methods of data analysis used (multiple imputation/only available data and deaths	This study demonstrates that Bort is superior to High Dex for the treatment of relapsed MM in

Table 2 (continued)

Authors	Patients included in the PRO analysis[a]	Timing of PRO assessment	PRO instrument/s	Statistically and clinically meaningful PRO outcomes[b]	Treatment recommendations by the authors
2005 and 2007	FACT/GOG-NTX analysis			assigned the worst possible scores/deaths treated as withdrawals or missing data[d]) demonstrated that Bort is associated with better HRQoL than High Dex across multiple domains: EORTC QLQ-C30 GHS, Physical Functioning, Role Functioning, Cognitive Functioning, Emotional Functioning, Social Functioning, Pain, Dyspnoea, Insomnia and FACT/GOG-NTX	patients who have received one to three previous therapies other than Bort. The results show that Bort was associated with significantly better multidimensional HRQoL compared with Dex, consistent with the better clinical outcomes seen with Bort
Dubois D. et al.; Viala M et al.; Richardson PG et al.	144	Patients completed the PRO instruments during screening, on day 1 of cycles 3, 5 and 7 of treatment as well as at the end of the study	EORTC QLQ-C30 FACT/GOG-NTX EORTC QLQ-MY24 FACIT-Fatigue	Mixed outcome: MID, more than 35% of patients reported improvement greater than 5 or 3 points in: FACIT-Fatigue and EORTC QLQ-C30 GHS, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning and Fatigue scales; EORTC QLQ-MY24 Disease Symptoms, Social Support and Future Perspective scales	Bort induces clinically significant responses, with manageable toxic effects, in RRMM patients. A RCT comparing Bort with High Dex in patients with relapsed MM is ongoing. The results of this trial and other ongoing studies should provide clinical guidance as to how to use this agent in earlier-stage disease. This study demonstrated the complementary value for PRO assessments in further interpreting clinical response, the impact of adverse effects, and patient prognosis in clinical trials
Waage A et al.	62/65 patients completed the 1st questionnaire, 38/47 patients alive completed the 12 wk questionnaire and 20/41 the questionnaire at 24 wk	Patients were asked to complete the questionnaire prior to treatment and at 12 and 24 weeks of follow-up	EORTC QLQ-C30	Symptoms only: Pain improved of 15 points and Constipation increased of 32 on the 0–100 scale (differences or changes of 10 or more points were regarded as clinically significant)	We did not find a relationship between Thal concentration and effect after 12 wk. However, our study was not specifically designed to detect such a concentration– effect relationship. The lack of relationship in our study therefore does not exclude that such a relationship exists

ALCAR acetyl-L-carnitine; *BDD-A* bortezomib, doxorubicin, dexamethasone plus acetyl-L-carnitine; *Bort* bortezomib; *BPI-SF* Brief Pain Inventory-Short Form; *CFZ* carfilzomib; *Dex* dexamethasone; *EORTC QLQ-C30* European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; *EORTC QLQ-CIPN20* European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy; *EORTC QLQ-MY* European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Multiple Myeloma Module; *EQ-5D* EuroQoL-5 Domains; *FACIT* Functional Assessment of Chronic Illness Therapy; *FACT/GOG-NTX* Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; *GHS* Global Health Status/QoL scale; *HRQoL* health-related quality of life; *Len* lenalidomide; *MID* minimal important differences; *PFS* progession-free survival; *PN* peripheral neuropathy; *Pom* pomalidomide; *PROs* patient-reported outcomes; *RCT* randomized controlled trial; *RRMM* relapsed refractory multilple myeloma; *Thal* thalidomide; *wk* week

[a] Data are number of patients (%)

[b] Symptoms only/Functional scale only/Global health status-QoL scale only: if a statistically and/or clinically meaningful difference between treatment arms (if more than one) or from baseline (if single arm trial) at any time point is found in either a symptom single item or a symptom scale/in any of the five functional scale/in the global QoL scale. Mixed outcome: if a combination of two or three of the above reported categories is found at any time point during the study period. Study equivalence: if no statistically and/or clinically meaningful difference between treatment arms (if more than one) or from baseline (if single arm trial) at any time point during the study is found

[c] "Future perspective" is not considered a functional scale but, choosing from the types of outcomes listed above, we decided that the more appropriate category for this domain is "Functional scale only "

[d] Only the domains that reported statistically meaningful difference by, at least, two of the four different methods of data analysis were selected

than those reported in the control group. Based on toxicity data, we may have expected carfilzomib, ixazomib, pomalidomide, bortezomib, and elotuzumab to cause an impairment on patient's HRQOL. Instead, these therapies were associated, in the same RCT, with improved PRO outcomes or, in the case of elotuzumab and ixazomib, with no differences in PRO. For example, pomalidomide was associated with higher percentages of fatigue measured by CTCAE but, from the patient's perspective, the same therapy was associated with improved outcomes. In the APEX trial, patients in the bortezomib group reported better outcomes in nausea, diarrhea, and neurotoxicity but this was not reflected in toxicity results. In TOURMALINE-MM1 study [42], physicians reported higher percentages of nausea and vomiting in the ixazomib group, while the same symptoms were similar between treatment arms when reported by patients themselves. This emphasizes the added value of taking into consideration the patients' perspectives and the importance of PRO in the evaluation of treatment effectiveness. Focusing attention only on measures such as toxicity, which are typically based on laboratory information or physician's judgements, may provide a partial view of overall treatment effectiveness. As RRMM patients are vulnerable population, often characterized by low survival rates, a more systematic implementation of PRO assessment may provide novel additional information to more robustly inform patient care.

This study has limitations. Although we used a comprehensive key search strategy, it is possible that we have missed some studies. Furthermore, the exclusion of non-English-language published papers from this review may have decreased the number of studies examined, but is unlikely that the quality of the review has been reduced [50]. The strength of our study was the analysis and inclusion of most recent studies that take into consideration novel drugs approved for RRMM patients.

In conclusion, there is paucity of evidence-based data on PRO in RRMM patients. The management of patients who have already received prior treatments represents a major challenge, as treatment options are continuously increasing. There is urgent need to implement PRO assessment in forthcoming studies in this area to more comprehensively evaluate treatment effectiveness.

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Compliance with ethical standards

Conflict of interest FE: Research funding (Lundbeck, TEVA and Amgen); Consultant/Advisory Role (Bristol-Myers Squibb, Seattle Genetics, TEVA and Incyte)

MC: Remuneration (Janssen, Celgene, Amgen, Takeda, Bristol-Myers Squibb), Consultant/Advisory Role (Janssen, Celgene, Amgen, Takeda, Bristol-Myers Squibb)

TC: Consultant/Advisory Role (Janssen-Cilag, Celgene, Amgen, Takeda, Bristol-Myers Squibb)

The remaining authors have no conflicts of interest.

I have full control of all primary data and I agree to allow the journal to review their data if requested.

Appendix 1

("quality of life" OR "health-related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social" OR "social functioning" OR "social well-being" OR "patient-reported symptom" OR "patient-reported outcomes" OR pain OR fatigue OR "patient-reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR "performance status" OR nausea OR functioning OR vulnerability OR fragility OR bone OR bone pain OR skeletal fracture OR weakness OR renal insufficiency OR anemia OR infections OR numbness OR tingling OR lesions OR hypercalcemia OR hyperviscosity OR bleeding) AND Myeloma AND (Relapsed OR Refractory).

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