Tolerability of Treatments for Relapsed or Refractory Multiple Myeloma: A Systematic Review

Abstract PF726

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INTRODUCTION

- Multiple Myeloma (MM) is an incurable, terminal hematologic cancer of unknown etiology that results in the production of abnormal blood plasma cells.[1]
- Due to the natural history of MM, almost all patients eventually relapse or become resistant to therapy.[2]
- Yet, treatment options for patients with relapsed/refractory multiple myeloma (RRMM) are limited, and consideration must be made to several clinical factors, including disease severity and aggressiveness, response to prior lines of therapy, patients' age and fitness, and the presence of comorbidities.[2,3]

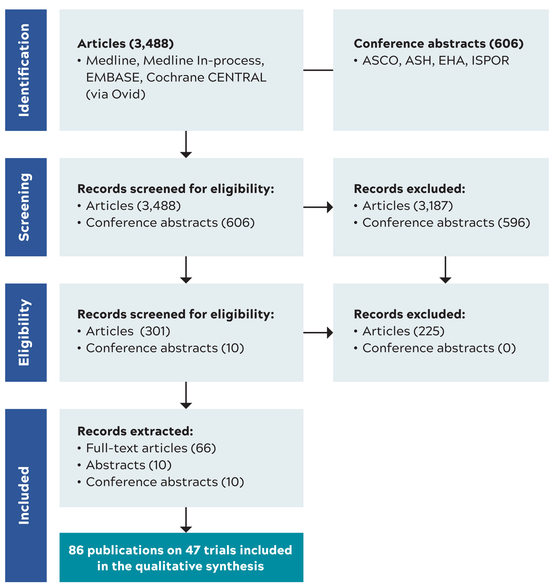
OBJECTIVE

- The objective of this study was to conduct a systematic literature review (SLR) of the tolerability of treatments for RRMM.

METHOD

- The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[4]
- We employed the following eligibility criteria
  - Population: Patients with RRMM (≥ 18 years of age)
  - Intervention/Comparators: Pharmacological and non-pharmacological treatments for RRMM
  - Outcomes: Grade 3 and 4 adverse events (AEs); treatment discontinuation (all-cause, and due to AEs, respectively)
  - Study design: Randomized controlled trials (RCTs) reporting outcomes of interest in patients with RRMM (phase 1 RCTs, pharmaco-economics, pharmacokinetics and pharmacodynamics studies, reviews, and comments/letters were excluded)
  - Date and language restrictions: Full-text records published between January 2008 and October 2018 (date of search) in English, and conference proceedings published between 2017 and 2018 in English
- Following study selection, all relevant data from eligible studies were extracted as reported by the study

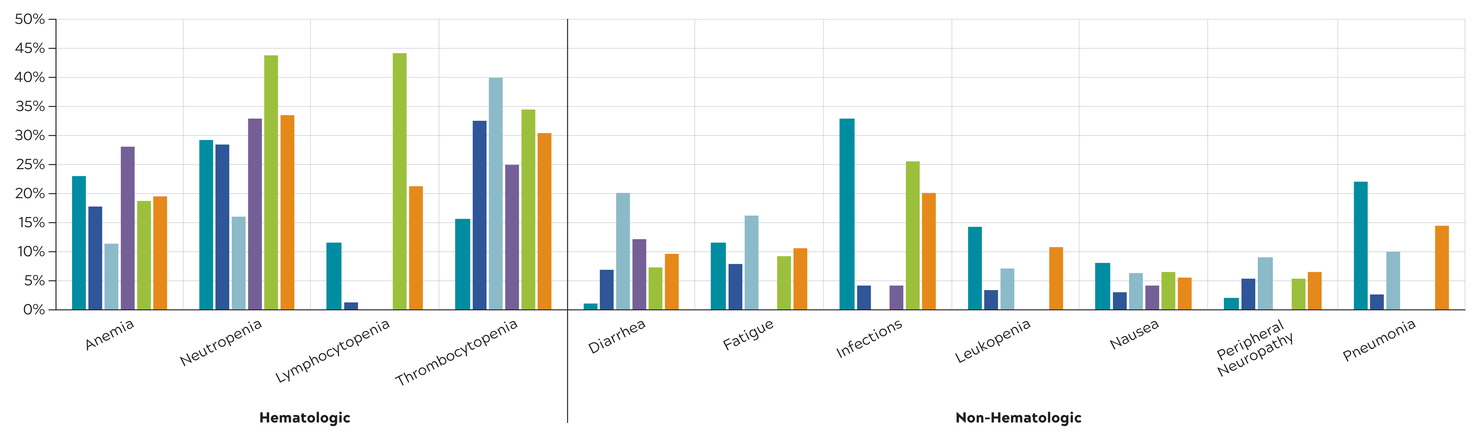
Figure 1. Study selection



RESULTS

- In total, 76 articles and 10 conference abstracts reporting results from 47 RCTs were identified in the search (**Figure 1**), of which 67 studies reported safety outcomes in RRMM.
- Identified RCTs involved an average of 430 patients (range: 22 to 929) and covered a total of 24 interventions from 12 different drug classes for RRMM.
- The most widely studied group of interventions were proteasome inhibitors (PIs), monoclonal antibodies (mAbs), and immunomodulatory drugs (IMiDs), represented in 44%, 22% and 15% of the studies, respectively.
- The most frequent AEs associated with treatments of RRMM are presented in **Figure 2** (by drug class) and in **Table 1** (by drug class and subgroup). AEs with grades >3 with a 10% cutoff were selected; and categorized by intervention and drug class as well as mono- or combination therapies for each treatment arm of studies reporting safety outcome of interest.
- While neutropenia, thrombocytopenia and anemia were the highest and most commonly reported AEs in almost all investigated interventions, there were some differences within the drug classes (see **Table 1**).

Figure 2. Most frequent AEs (grades >3) - by drug class



Frequency of grade >3 adverse events with a 10% cutoff reported in at least two interventions (average of max)

Table 1. Overview of most commonly reported AEs (grades >3) by drug class and subgroup

Intervention/AEs	Hematologic AEs						Non-Hematologic AEs					
	Anemia		Neutropenia		Thrombocytopenia		Diarrhea		Infection		Fatigue	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
IMiDs	THA: 6%	POM: 40%	THA: 7%	POM: 52%	THA: 2%	POM: 29%	POM: 1%	THA: NR	POM: 33%	THA: NR	THA: 11%	POM: 12%
PIs	BTZ/IXA: 12%	CAR: 25%	IXA: 22%	CAR: 32%	IXA: 19%	BTZ: 55%	CAR: 5%	BTZ: 10%	CAR: 13%	BTZ: 17%	IXA: 4%	BTZ: 11%
Pan-HDACs	VOR: 7%	PAN: 16%	PAN: NR	VOR: 16%	VOR: 23%	PAN: 57%	VOR: 16%	PAN: 24%	NR	NR	PAN/VOR: 16%	PAN/VOR: 16%
Alkylating agents	MP: 20%	BEN: 36%	MP: 2%	BEN: 64%	MP: 7%	BEN: 43%	MP: 12%	BEN: NR	MP: 4%	BEN: NR	NR	NR
mAbs	TAB: 12%	DAR: 24%	ELO: 36%	DAR: 52%	ELO: 21%	SIL: 48%	DAR: 5%	ELO/TAB: 8%	SIL: 16%	ELO: 35%	DAR: 6%	TAB: 11%
Subgroups	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Monotherapies[a]	23%	46%	19%	48%	20%	38%	5%	5%	2%	13%	7%	11%
Combination therapies	18%	40%	25%	52%	30%	57%	8%	24%	8%	35%	9%	16%

[a]Only included an intervention without dexamethasone
AE: adverse event; BTZ: bortezomib; BEN: bendamustine; CFZ: carfilzomib; DAR: daratumumab; ELO: elotuzumab; IMiDs: immunomodulatory agents; IXA: ixazomib; mAbs: monoclonal antibodies; MP: melphalan; NR: not reported; PAN: panobinostat; Pan-HDACs: histone deacetylase inhibitors; PEM: pembrolizumab; PIs: proteasome inhibitors; POM: pomalidomide; SIL: siltuximab; TAB: tabalumab; THA: thalidomide; VOR: vorinostat.
Note: The following interventions are not approved for RRMM by FDA and EMA: tanespimycin, plitidepsin, oblimersen, pembrolizumab, siltuximab, tabalumab and vorinostat. Circularly permuted TRAIL is not approved for the treatment of MM in the EU. These compounds appeared in 8 of the 86 studies selected.

HEMATOLOGIC AEs

- Neutropenia was as low as 2-7% for THA and MP compared to 52-64% for POM, DAR and BEN.
- Thrombocytopenia was highest for DAR, SIL, BTZ and PAN (45-57%) in comparison to MP and THA (2-7%).

NON-HEMATOLOGIC AEs

- The frequency of diarrhea was particularly high in pan-HDAC inhibitors (PAN 24% and VOR 16%) compared to IMiDs, mAbs and PIs (1-10%).
- Infections were also commonly reported ranging from 35% for ELO and 33% for POM compared to 16% for SIL and 13% for CAR.

SUBGROUPS – MONO- AND COMBINATION THERAPY

- Reported rates of AEs were similar between monotherapies and combination therapies. The largest difference for the most frequently reported AEs were in those for diarrhea and infection.
- Combination therapies seem to generate slightly higher frequency of AEs with exception of anemia.

TREATMENT DISCONTINUATION

- Treatment discontinuation (all causes) was reported in between 16% and 100% (average 73%); ranging within drug classes from 71% for mAbs and for 86% for IMiDs.
- Discontinuation due to AEs was reported between 3% and 51% (average 18%); ranging within drug classes from 9% for mAbs and 26% for pan-HDAC inhibitors.

LIMITATIONS

- Data needs to be interpreted with caution as this is an average of all interventions within drug classes, as well as not all studies reported detailed safety data or safety data at all. Our study had further limitations: the majority of the studies had an open-label study design which may introduce risk of bias. Not all publications reporting imbalances in baseline characteristics have conducted a sensitivity analysis to control for baseline differences. The approaches to data analysis methods have varied across studies. Not all publications have reported on compliance rates in both treatment arms.

CONCLUSIONS

- Current therapies for RRMM are associated with several serious adverse events, resulting in treatment discontinuation.
- Most common hematologic AEs were neutropenia (33% [2-64%]), thrombocytopenia (30% [2-57%]), and anemia (19% [6-40%]); the most common non-hematologic AEs were infection (20% [4-35%]), fatigue (11% [4-16%]) and diarrhea (10% [1-24%]).
- Monotherapies tend to have a better safety profile in most hematologic and non-hematologic AEs apart from anemia compared to combination therapy, even though not statistically significant.
- Yet, the outcomes of our review show that tolerability profiles vary markedly between interventions and patient populations.

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DISCLOSURES

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