A review of treatment effect modifiers and/or prognostic factors included in unanchored indirect treatment comparisons involving triple-class exposed relapsed/refractory multiple myeloma

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Introduction

- Patients with relapsed/refractory multiple myeloma (RRMM) previously treated with an immunomodulatory agent, proteasome inhibitor, and anti-CD38 monoclonal antibody (ie, those who are triple-class exposed [TCE]) have poor clinical outcomes and there is no uniform standard of care (SOC)[1-3]
- However, the treatment landscape for TCE RRMM is rapidly evolving, although there are few head-to-head trials for these emerging treatment options
- Indirect treatment comparisons (ITCs) can be used to synthesize evidence and estimate the relative efficacy of competing interventions evaluated in the absence of head-to-head trials, which may support treatment decision making
- Unanchored ITCs may be used to compare treatment arms between single-arm trials and/or observational studies that do not share a common comparator, and these should be adjusted for appropriate effect modifiers and prognostic variables to avoid bias[4]
- Since the previous review of ITCs in RRMM,[4] new treatments with various mechanisms of action have been approved and many treatments have been compared via unanchored ITCs (single-arm trial designs); therefore, an updated review was performed

Objective

- To update a review of published ITCs to identify the latest effect modifiers and/or prognostic factors included in published unanchored ITCs for TCE RRMM to inform covariate selection processes

Methods

- To identify published unanchored ITCs comparing the efficacy of treatments for patients with TCE RRMM, MEDLINE® and Embase® were searched in July 2022
- Manual searches of the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), and European Hematology Association (EHA) conferences were performed from January 2020 to July 2022
- Predefined search terms were restricted to population and study design terms only
  - The selection criteria and search strategies were adapted from the previous review of ITCs in RRMM,[4] which searched references from September 2017; the current update was restricted to studies published since then to July 2022
- Included studies must have evaluated a pharmacologic intervention for the treatment of TCE RRMM
  - Reported on at least overall response rate, duration of response, progression-free survival, or overall survival
  - Performed anchored or unanchored between-study comparisons, including network meta-analysis, multiple/mixed treatment comparisons, matching-adjusted indirect comparisons, simulated treatment comparisons, outcome regression, and propensity score weighting (or doubly-robust methods)
- Data were extracted for publication type, trial characteristics (population, sample size, and data type); analysis type (base case/sensitivity); characteristics adjusted by population subsetting or as model covariates; outcome data availability; covariate selection process; and effective sample size

Results

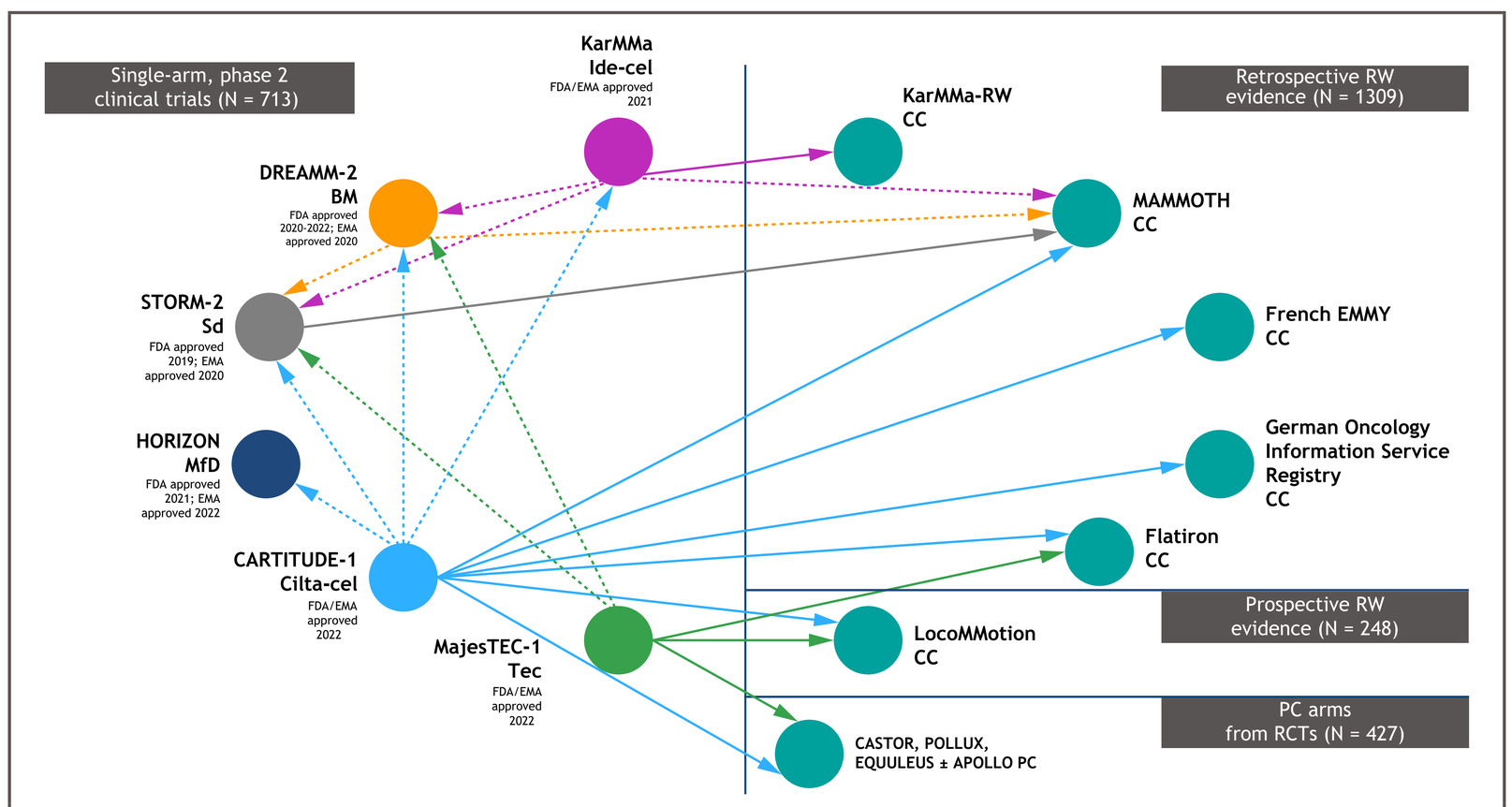
Evidence base

- A total of 37 unanchored ITCs in TCE RRMM were identified, representing 22 unique comparisons involving the following studies: CARTITUDE-1 (N = 10), MajesTEC-1 (N = 5), KarMMa (N = 4), DREAMM-2 (N = 2), and STORM-2 (N = 1) (**Figure 1**)
  - No anchored ITCs were published as new drug approvals for TCE RRMM were based on evidence from single-arm clinical trials
- These analyses included comparisons with 16 different target populations within TCE RRMM studies, including external populations in single-arm clinical trials, RW studies, and pooled SOC arms from RCTs
- Out of the 22 unique comparisons:
  - 12 were IPD analyses of single-arm trials and 10 were IPD versus AD for single-arm trials
  - 9 were single-arm versus single-arm trials and 13 were single arm versus RW data or SOC arms from RCTs
- The most common external populations for comparison were MAMMOTH (N = 4), STORM-2 (N = 4), and DREAMM-2 (N = 3)
  - Of note, comparisons with the same external study included different target populations
  - For example, comparisons to MAMMOTH included the full treated population (N = 249) versus penta-class exposed/triple-class refractory patients (N = 128), or patients that did not have disease progression/death within 47 days (N = 95)

Prognostic factors/effect modifiers

- Patient characteristics were restricted to population subgroups in 8/22 (36%) comparisons to better align the primary/external studies
  - The most common subgroups were defined based on refractory status (N = 6; triple-class refractory, last line of therapy, or daratumumab) and exposure status (N = 3; penta-class exposure)

Figure 1. Evidence base of unanchored ITCs in TCE RRMM



The direction of each arrow points towards the target population for the unanchored ITC. A solid line indicates an IPD-IPD analysis while a dashed line indicates an IPD-AD analysis.
Different color lines were used for each trial of interest.
PC arms included: bortezomib + dexamethasone; lenalidomide + dexamethasone; daratumumab + carfilzomib + dexamethasone; pomalidomide + dexamethasone.
AD, aggregate data; BM, belantamab mafodotin; CC, conventional care; Cilta-cel, ciltacabtagene autoleucel; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ide-cel, idecabtagene vicleucel; IPD, individual patient data; MfD, melphalan flufenamide + dexamethasone; PC, physician's choice; RCT, randomized controlled trial; RW, real world; Sd, selinexor + dexamethasone; Tec, teclistamab.

- Base-case analyses (N = 22) included between 3 and 15 covariates, most commonly adjusting for refractory status (N = 20), number of prior lines (N = 18), International Staging System (ISS)/Revised ISS (R-ISS) disease stage (N = 18), and cytogenetic risk profile (N = 16) (**Table 1**)
- In sensitivity analyses, covariates most often adjusted for were sex (N = 12), race (N = 10), age (N = 9), prior stem cell transplantation (N = 7), and ECOG PS (N = 7) (**Table 1**)
- 11/22 (50%) analyses reported information on the covariate selection process
  - Prognostic factors were identified based on: a literature review with clinical opinion (N = 9), clinical opinion alone (N = 2), univariate models (N = 2), and/or exploratory analyses (N = 1)
  - In 4 analyses, clinical experts were provided with information on how factors differed between the primary trial and external study
  - Only 5 analyses ordered covariates, all involving full-text CARTITUDE-1 comparisons
- The median number of covariates across the 22 ITCs was 6.5
  - Of note, the number of covariates was inconsistent for analyses involving the same primary trial, as the number of included covariates was impacted by access to IPD/data availability for the external AD study
  - 8 analyses included < 6 covariates in the base-case model (involving CARTITUDE-1 comparisons)

Table 1. Patient characteristics adjusted for in unanchored ITCs in TCE RRMM

Prognostic factor/effect modifier	Adjusted for in unanchored ITCs	
	Base case	Sensitivity
Refractory status (number of therapies)	20	0
Exposure status (number of therapies)	18	4
ISS/R-ISS disease stage	18	0
Cytogenetics risk profile	16	1
Time since diagnosis	14	5
Extramedullary disease	13	0
Age	12	9
Time to progression on last regimen	9	0
ECOG PS	7	7
Sex	6	12
Prior stem cell transplantation	5	7
Exposure to specific agents	5	0
Hemoglobin	4	2
Creatinine clearance	4	2
Duration of prior therapy	4	0
Multiple myeloma type/immunoglobulin type	3	2
Lactate dehydrogenase	2	0
Race	1	10

ECOG PS, Eastern Cooperative Oncology Group performance status.

Model diagnostics

- Effective sample size values were reported for 13/22 (60%) analyses, ranging from 33 to 248 in base-case analyses
- None of the unanchored ITCs assessed the structural uncertainty in the results (ie, assessment of different combinations of covariates of interest)

Discussion

- During the past 5 years alone, 22 unanchored ITCs have been performed in TCE RRMM based on only 6 single-arm clinical trials evaluating 6 new treatments and various comparisons to 7 RW/SOC studies, despite the rapid evolution of the treatment landscape
  - The target population is unique to each comparison; therefore, the comparability of these analyses is influenced by different underlying patient populations to the external target populations
- A list of rank-ordered prognostic factors was reported for CARTITUDE comparisons, although it did not include bridging therapy (eg, proportion of patients receiving or responding to bridging therapy, or bridging therapy regimen options), which may be an important prognostic factor in comparisons of chimeric antigen receptor T cell therapies
- Covariate counts in this review are influenced by the number of comparisons for the trial of interest (and therefore may be affected by how often a trial is compared with an external study) as well as data availability based on access to IPD versus AD
- For the current evidence base, it is challenging to evaluate multiple treatment comparisons in a cohesive framework due to:
  - Inconsistencies in patient populations from the same external studies (ie, full populations versus subgroups)
  - Inconsistencies included covariates for adjustment
  - Reuse of IPD from single-arm clinical trials without accounting for correlations

Conclusions

- There are important differences in unanchored ITCs evaluating comparative efficacy and safety of treatments for TCE RRMM, eg, the target population of interest, number of covariates, and covariates adjusted for, limiting or preventing the comparison of results across analyses
- The most common effect modifiers and/or prognostic factors adjusted for in unanchored ITCs in TCE RRMM were refractory status, number of prior lines, disease stage, and cytogenetic risk profile
- Improved transparency for unanchored ITCs is required, reporting covariates identified a priori, impact of structural uncertainty in terms of different covariate combinations, and factors not feasible to adjust for in the analysis that may have biased results

References

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Supplemental references are available in the ISPOR Europe 2023 conference app

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