Association between response rates and survival outcomes in patients with newly diagnosed multiple myeloma. A systematic review and meta-regression analysis

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Abstract

Objectives: We performed a systematic review and meta-regression analysis of randomized control trials to investigate the association between response to initial treatment and survival outcomes in patients with newly diagnosed multiple myeloma (MM).

Methods: Response outcomes included complete response (CR) and the combined outcome of CR or very good partial response (VGPR), while survival outcomes were overall survival (OS) and progression-free survival (PFS). We used random-effect meta-regression models and conducted sensitivity analyses based on definition of CR and study quality.

Results: Seventy-two trials were included in the systematic review, 63 of which contributed data in meta-regression analyses. There was no association between OS and CR in patients without autologous stem cell transplant (ASCT) (regression coefficient: .02, 95% confidence interval [CI] −0.06, 0.10), in patients undergoing ASCT (−.11, 95% CI −0.44, 0.22) and in trials comparing ASCT with non-ASCT patients (.04, 95% CI −0.29, 0.38). Similarly, OS did not correlate with the combined metric of CR or VGPR, and no association was evident between response outcomes and PFS. Sensitivity analyses yielded similar results.

Conclusions: This meta-regression analysis suggests that there is no association between conventional response outcomes and survival in patients with newly diagnosed MM.

KEYWORDS
complete response, meta-regression analysis, multiple myeloma, survival, systematic review

1 | INTRODUCTION

Multiple myeloma (MM) accounts for more than 10% of hematologic malignancies and is characterized by clonal plasma cell proliferation and overproduction of monoclonal paraprotein.1 Despite remaining an incurable disease, the introduction and widespread use of novel drugs in addition to enhanced understanding of the disease biology have led to higher response rates and improved life expectancy of patients with MM over the past decade.2

Complete response (CR) and very good partial response (VGPR) are common outcomes used in MM research for evaluating treatment efficacy.2,4 Individual studies have associated CR with extended survival and better progression-free survival (PFS), but not necessarily with overall survival (OS),5-10 while a recent
meta-analysis of prospective and retrospective studies suggests a positive association of CR post autologous stem cell transplantation (ASCT) during the first-line therapy with PFS and OS outcomes. Notably, given that most patients relapse despite achieving CR, data from two meta-analyses suggest that minimal residual disease (MRD) status is a valid surrogate outcome for both OS and PFS in patients with MM, including those who have achieved CR. As a result, the International Myeloma Working Group (IMWG) has issued guidelines for defining new response categories, based on MRD, that identify responses deeper than those conventionally defined as CR.

In light of accumulating data from long-term trials, we sought to update the evidence base regarding the association between response to induction therapy and survival outcomes, through a systematic review and meta-regression analysis of randomized controlled trials (RCTs) in patients with newly diagnosed MM.

## METHODS

We report our review in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

### Eligibility criteria

We searched for RCTs that compared induction therapies for MM and reported results on CR and survival outcomes. To reduce the effect of previous therapies, we included solely trials recruiting newly diagnosed patients or patients previously treated with corticosteroids alone. Studies were eligible irrespective of type of induction therapy, including both trials that assessed therapies followed by ASCT and trials with patients not undergoing ASCT.

### Data sources and searches

We conducted a comprehensive search of Embase, MEDLINE, Evidence-Based Medicine Reviews and Cochrane Central Register of Controlled Trials from inception to April 2015, without imposing any language restrictions. Relevant controlled vocabulary and free text terms were combined with a search filter for identifying RCTs. The detailed strategy is presented in Table S1. On December 2015, we updated our search, to identify any full-text publications for reports that had been identified as abstracts in our initial search.

### Study selection

We performed study selection using an internet-based software (Covidence systematic review software). Each individual report was screened by two reviewers independently, based on prespecified eligibility criteria, first at title and abstract level and subsequently in full text. Conflicts were resolved by consensus or were arbitrated by a third reviewer. In case of multiple publications of the same trial, we collated data from all relevant reports.

### Data extraction

Data from eligible studies were extracted in duplicate by two independent reviewers, using a software-based form (Covidence). We extracted data on study and patients’ characteristics, interventions (study drugs and doses) and outcome metrics. Response outcomes included CR and the combined outcome of CR or VGPR, while survival outcomes were OS and PFS. We extracted relative risks (RRs) and 95% confidence intervals (CIs) for response outcomes. For survival outcomes, we extracted data on the basis of a predefined hierarchy as follows: (i) hazard ratios (HR), (ii) adjusted risk ratios (RR) and (iii) RR at: (a) 5, (b) 3 or (c) 2 years. If a study did not report any of these metrics but provided survival curves, we calculated HRs or RRs using appropriate software. For all outcomes, we abstracted the exact definition used in each trial. In trials that included ASCT patients, CR and VGPR data were extracted following ASCT. In case of a study not reporting PFS data, we utilized data for event-free survival instead.

### Risk of bias assessment

We assessed methodological quality of included studies using the Cochrane Risk of Bias tool for RCTs. Two independent reviewers assessed risk of bias due to randomization sequence, allocation concealment, blinding, incomplete outcome data, selective reporting, and funding. We determined overall strength of evidence by means of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

### Statistical analysis

Random-effect meta-regression models were used to assess the association between the log-transformed RR of CR or (CR or VGPR) (independent variables) and the log-transformed HR of OS or PFS. Meta-regression results were expressed as a regression coefficient, 95% CI and a P value. The coefficient quantifies the magnitude of increase in the log-transformed HR of survival outcomes associated with one-unit increase in the log-transformed RR of response outcomes. A value of 0 indicates no relationship between two variables, whereas values of 1 or −1 represent maximum positive and negative relationship, respectively. A two-tailed P value lower than .05 was deemed statistical significant. We assessed heterogeneity of results using the I² statistic. All statistical analyses were conducted using Stata version 14.1 (StataCorp LLP, College Station, TX, USA).

We conducted separate analyses, based on whether studies recruited patients undergoing ASCT or not. To explore the effect of variation in definition of CR, we performed a sensitivity analysis including only trials that utilized the CR definition suggested by the IMWG or the European group for Blood and Marrow Transplant (EBMT) guidelines. In a similar manner, for the combined metric of CR or VGPR, we conducted a sensitivity analysis with trials that used either the IMWG or the EBMT definition for CR and reported
VGPR data, using a definition consistent with the one suggested by the IMWG guidelines. In addition, we conducted a sensitivity analysis restricted to studies that were deemed at low overall risk of bias.

3 | RESULTS

3.1 Search results and study characteristics

The study selection process is depicted in Figure 1. Our initial search identified 4043 relevant reports. After screening titles and abstracts, 434 reports were assessed at full text. A total of 72 trials were included in the systematic review, most of which (46 trials) recruited non-ASCT patients, while eleven studies assessed regimens in patients undergoing ASCT, and nine compared induction regimens versus ASCT. In addition, five trials compared single with double ASCT. A complete list of references of included studies is available in Appendix S1.

Characteristics of all eligible studies are presented in Table S2. Seven studies, which were identified as abstracts, did not provide adequate outcome data to be incorporated in the meta-regression analysis (mostly ongoing studies), while for studies comparing single versus double ASCT, meta-regression analysis was also not possible due to limited number of studies.

3.2 Risk of bias in included studies

Risk of bias assessment is listed in Table S3. Randomization sequence and allocation concealment were poorly reported in most studies. Most studies were open label and had received funding from pharmaceutical industry. Overall, risk of bias was low in 20 trials and unclear in 27 studies, whereas 32 trials were at high risk of bias mainly due to lack of allocation concealment or incomplete outcome data for CR and OS.

3.3 Overall survival

There was no association between OS and CR in patients without ASCT (regression coefficient 0.02, 95% CI −0.06, 0.10). Similarly, no association was evident for patients undergoing ASCT (−0.11, 95% CI −0.44 to 0.22) and in trials comparing ASCT with non-ASCT patients (0.04, 95% CI −0.29, 0.38). Overall survival did not correlate with the combined metric of CR or VGPR in either of the three subcategories of studies (Table 1).

3.4 Progression-free survival

Meta-regression analyses of non-ASCT trials did not demonstrate a correlation of PFS with CR (−0.01, 95% CI −0.16, 0.14) or with (CR or VGPR) (0.04, 95% CI −0.22, 0.3). Regression coefficient values were also nonsignificant in all PFS analyses, both for ASCT trials and for studies comparing ASCT with non-ASCT regimens (Table 1).

3.5 Sensitivity analyses

Overall, 42 studies utilized the definition for CR suggested by the IMWG or the EBMT. Sensitivity analyses restricted to these studies did not demonstrate any association for OS or PFS with either CR or (CR or VGPR). Finally, utilizing only studies at low risk of bias (19 studies) did not affect results in analyses for all outcomes, both for non-ASCT and for ASCT patients (Table 1).

3.6 Strength of evidence

Results were precise in most analyses; however, heterogeneity was high due to wide variation in treatment regimens. Indirectness was low, as external validity of our results is expected to be high. Overall, as a non-randomized observation of an association our results would warrant low certainty based on GRADE approach.

4 | DISCUSSION

In our analysis, we explored the relationship between response to initial treatment and survival in patients with newly diagnosed MM,
TABLE 1 Results of meta-regression analyses for response and survival outcomes

<table>
<thead>
<tr>
<th>Response outcome</th>
<th>Type of studies</th>
<th>Overall survival (Coefficient (SE) 95% CI)</th>
<th>Progression-free survival (Coefficient (SE) 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I² (%)</td>
<td>I² (%)</td>
</tr>
<tr>
<td><strong>Main analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Non-ASCT</td>
<td>.02 (.04) -0.06 to 0.10 66.82</td>
<td>-.01 (.07) -0.16 to 0.14 86.40</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>-.11 (.15) -0.44 to 0.22 62.92</td>
<td>-.28 (.21) -0.76 to 0.19 78.81</td>
</tr>
<tr>
<td></td>
<td>ASCT vs non-ASCT</td>
<td>.04 (.14) -0.29 to 0.38 83.59</td>
<td>.06 (.11) -0.21 to 0.33 77.96</td>
</tr>
<tr>
<td>CR or VGPR</td>
<td>Non-ASCT</td>
<td>.05 (.06) -0.08 to 0.17 68.54</td>
<td>.04 (.12) -0.22 to 0.30 88.59</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>-.26 (.17) -0.69 to 0.16 37.57</td>
<td>-.45 (.22) -0.97 to 0.07 64.80</td>
</tr>
<tr>
<td></td>
<td>ASCT vs non-ASCT</td>
<td>.26 (.15) -0.22 to 0.74 66.23</td>
<td>.18 (.12) -0.22 to 0.57 72.52</td>
</tr>
<tr>
<td><strong>Sensitivity analysis of studies using IMWG or EBMT definitions for response outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Non-ASCT</td>
<td>.02 (.06) -0.10 to 0.13 70.50</td>
<td>-.01 (.09) -0.19 to 0.17 87.81</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>-.12 (.16) -0.50 to 0.25 68.14</td>
<td>-.21 (.24) -0.78 to 0.36 83.78</td>
</tr>
<tr>
<td></td>
<td>ASCT vs non-ASCT</td>
<td>-.04 (.1) -0.33 to 0.24 69.60</td>
<td>.05 (.13) -0.32 to 0.42 82.43</td>
</tr>
<tr>
<td>CR or VGPR</td>
<td>Non-ASCT</td>
<td>.07 (.07) -0.07 to 0.21 71.86</td>
<td>.04 (.13) -0.24 to 0.31 89.13</td>
</tr>
<tr>
<td></td>
<td>ASCT</td>
<td>-.14 (.09) -0.40 to 0.12 0</td>
<td>-.3 (.27) -0.99 to 0.38 80.06</td>
</tr>
<tr>
<td></td>
<td>ASCT vs non-ASCT</td>
<td>.09 (.17) -0.66 to 0.84 59.09</td>
<td>.14 (.17) -0.57 to 0.85 81.04</td>
</tr>
<tr>
<td><strong>Sensitivity analysis of studies at low overall risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Non-ASCT</td>
<td>.06 (.21) -0.45 to 0.56 80.88</td>
<td>-.17 (.12) -0.51 to 0.18 58.57</td>
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<td></td>
<td>ASCT</td>
<td>-.36 (.31) -1.35 to 0.63 68.01</td>
<td>-.62 (.3) -1.57 to 0.34 63.20</td>
</tr>
<tr>
<td>CR or VGPR</td>
<td>Non-ASCT</td>
<td>.27 (.25) -0.54 to 1.08 82.85</td>
<td>-.08 (.23) -1.06 to 0.90 82.66</td>
</tr>
</tbody>
</table>
|                  | ASCT           | NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA Na
for detecting MRD status. Moreover, as prognosis of MM can significantly differ based on patient’s genetic background (ie worse prognosis in patients with high-risk cytogenetics), future research should also focus on developing and validating novel phenotype and genotype indices. Finally, it is imperative that trials incorporate quality-of-life assessments alongside survival outcomes, considering that disease-related events and symptoms, as well as adverse effects of therapeutic interventions, can produce functional impairments and significantly affect patient’s lives through the course of the disease.

In conclusion, our systematic review and meta-regression analysis failed to demonstrate an association between response rates and survival of patients with newly diagnosed MM and question the use of CR as primary outcome in MM trials.

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CONFLICT OF INTEREST DISCLOSURES

SK has participated in advisory board and/or has received clinical research support by Celgene, Takeda, Abbvie, Novartis, Sanofi, Noxxon, Kesyos, Glycomimetics, Skyline Dx. EV has received honoraria from Novartis. The remaining authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

PP, AVM and MM conducted study selection. PP, AVM and TK performed data extraction. WZ and MHN conducted the analysis. AT, EV and MM prepared the first draft of the report, which was critically revised by all authors. All authors approved the final version of the manuscript. MM and AT supervised the study and are guarantors.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.
