Impact of high-risk disease on the efficacy of chimeric antigen receptor T-cell therapy for multiple myeloma: a meta-analysis of 723 patients

Chimeric antigen receptor (CAR) T-cell therapy showed enormously promising results in patients with relapsed or refractory multiple myeloma,[1,2] leading to approval of the first two products by the American Food and Drug Administration and the European Medicines Agency.[3,4] Current responses seem to be comparable across CAR T-cell products and trials (both commercial and academic), with an overall response of ~80%.[5] However, translation into sustained responses and thus, survival remain unclear, with relapse rates of ~45% among initial responders.

Despite the promises, CAR T-cell therapy is a very complex and expensive treatment, which poses challenges to healthcare systems and society in general.[6,7] Therefore, and in the wake of current efforts to study the effects of CAR T-cell therapy even in earlier lines of the treatment algorithm, patient selection becomes crucial. In this regard, the identification of high-risk patients is of utmost importance in order to be able to provide the most accurate counseling and choose the most effective treatment strategy that optimizes the outcome.[8] Recent analyses suggested that the incorporation of novel monoclonal antibodies such as daratumumab as a backbone for regimens in relapsed or refractory high-risk multiple myeloma, defined as the presence of t(4;14), t(14;16), or del(17p), may be associated with improved progression-free survival compared to that achieved with other regimens, while absolute outcome is still worse compared to that of patients with standard-risk features.[9] In contrast, for patients with other high-risk disease features such as extramedullary disease, results are still generally disappointing.[10] Sufficient reports on CAR T-cell therapy in these high-risk groups are lacking.

Here, we summarize the current body of evidence on the role of novel CAR-T cell therapies for relapsed or refractory multiple myeloma and high-risk disease, focusing on the identification of patients who may benefit and those who may not.

We performed a systematic literature review to identify all fully published prospective trials in accordance with current guidelines.[11] We searched Medline, EMBASE, Cochrane trials registry, and *www.clinicaltrials.gov*. A conventional meta-analysis was conducted using R statistical software.[5] Risk ratios and 95% confidence intervals (95% CI) were calculated within a random-effects framework using the Mantel-Haenszel method. Heterogeneity across trials was measured using I^2. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance. More than 50% is judged to show moderate heterogeneity, whereas >75% indicates severe heterogeneity.[11] The quality of evidence was documented according to the GRADE system, using the following levels of evidence: high, moderate, low and very low.[12] Because all trials conducted to date are non-randomized single-arm trials, the risk of bias was judged *a priori* to be serious.

The main efficacy outcomes were overall response rate, measurable residual disease, mortality, and relapse or progression. High-risk disease features were defined as the presence, at the time of CAR T-cell infusion, of cytogenetic high-risk, defined as at least either del(17p), t(14;16) or t(4;14), or disease-specific risk, defined as the presence of extramedullary disease or revised International Staging System (R-ISS) stage III disease.[13]

Out of a total of 769 screened articles, 17 trials comprising a total of 723 patients with heavily pretreated relapsed or refractory multiple myeloma were included in quantitative analyses (*Online Supplementary Figure S1*; all references are listed in the *Online Supplementary Appendix*). Overall, patients had received a median of five prior lines of treatment (such as proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies), including autologous stem cell transplantation in 51% of patients. The median age of the patients was 59 years (*Online Supplementary Table S1*).

The patients' characteristics, such as age and number of prior lines of therapy including autologous transplantation, were affected by trial origin. The median age and number of prior lines of therapy were 61 years and seven lines in USA-based trials *versus* 57 years and four lines in China-based trials. Ninety-two percent of patients had undergone autologous transplantation before receiving CAR T-cell therapy in USA/European trials, whereas only 28% of patients in China-led trials had undergone prior autografts.

The most frequent single target was B-cell maturation antigen (BCMA). Four trials used tandem CAR, including two trials targeting both BCMA and CD38 and two trials targeting both BCMA and CD19. One trial only targeted CD19. The co-stimulatory domain was 4-1BB in most trials, and fludarabine and cyclophosphamide constituted the most common lymphodepletion regimen.

Regarding disease risk and outcomes, extramedullary disease was not significantly associated with a worse overall response rate, showing a risk ratio of 0.97 (95% CI: 0.92-1.02; P=0.26). The quality of evidence was moderate (Figure

1A). In terms of depth of response, no significant association with measurable residual disease was observed (*P*=0.84), with a risk ratio of 0.93 (95% CI: 0.73-1.19); and the quality of evidence was moderate (*Online Supplementary Figure S1*). In contrast, in terms of progression-free survival, the presence of extramedullary disease was significantly associated with worse outcome, showing a risk ratio of 1.44 (95% CI: 1.24-1.67; *P*<0.001) in favor of patients without extramedullary disease. Thus, presence of extramedullary disease at the time of CAR T-cell therapy was associated with a 44% increased risk of relapse/progression or death after treatment, and the quality of evidence was moderate (Figure 1B). This also translated into significantly worse overall survival. The presence of extramedullary disease was associated with a 96% increased risk of death from any cause, showing a risk ratio of 1.96 (95% CI: 1.48-2.58; *P*<0.001) (*Online Supplementary Figure S1*). Furthermore, R-ISS stage III was significantly associated with a worse overall response rate (*P*<0.001).

In terms of cytogenetic risk and outcomes, a high-risk cytogenetic profile was significantly associated with worse overall response rate, showing a risk ratio of 0.86 (95% CI: 0.76-0.97) in favor of standard-risk cytogenetics (*P*=0.01). Correspondingly, the presence of high-risk cytogenetics at the time of CAR T-cell infusion was associated with a 14% increased risk of lack of response, and the quality of evidence was low (Figure 2A). For depth of response, the presence of high-risk cytogenetics appeared to be significantly associated with a 23% increased risk of measurable residual disease-positivity, showing a risk ratio of 0.78 (95% CI: 0.60-1.01; *P*=0.06) (*Online Supplementary Figure S1*). In terms of progression-free survival, high-risk cytogenetics were significantly associated with worse outcome, showing a risk ratio of 1.70 (95% CI: 1.29-2.25; *P*<0.001) in favor of standard-risk cytogenetics. Thus, the presence of high-risk cytogenetics was associated with a 70% increased risk of progression/relapse or death (Figure 2B). Correspondingly, high-risk cytogenetics were associated with significantly worse overall survival, showing a risk ratio of 2.11 (95% CI: 1.27-3.52; *P*=0.004) (*Online*

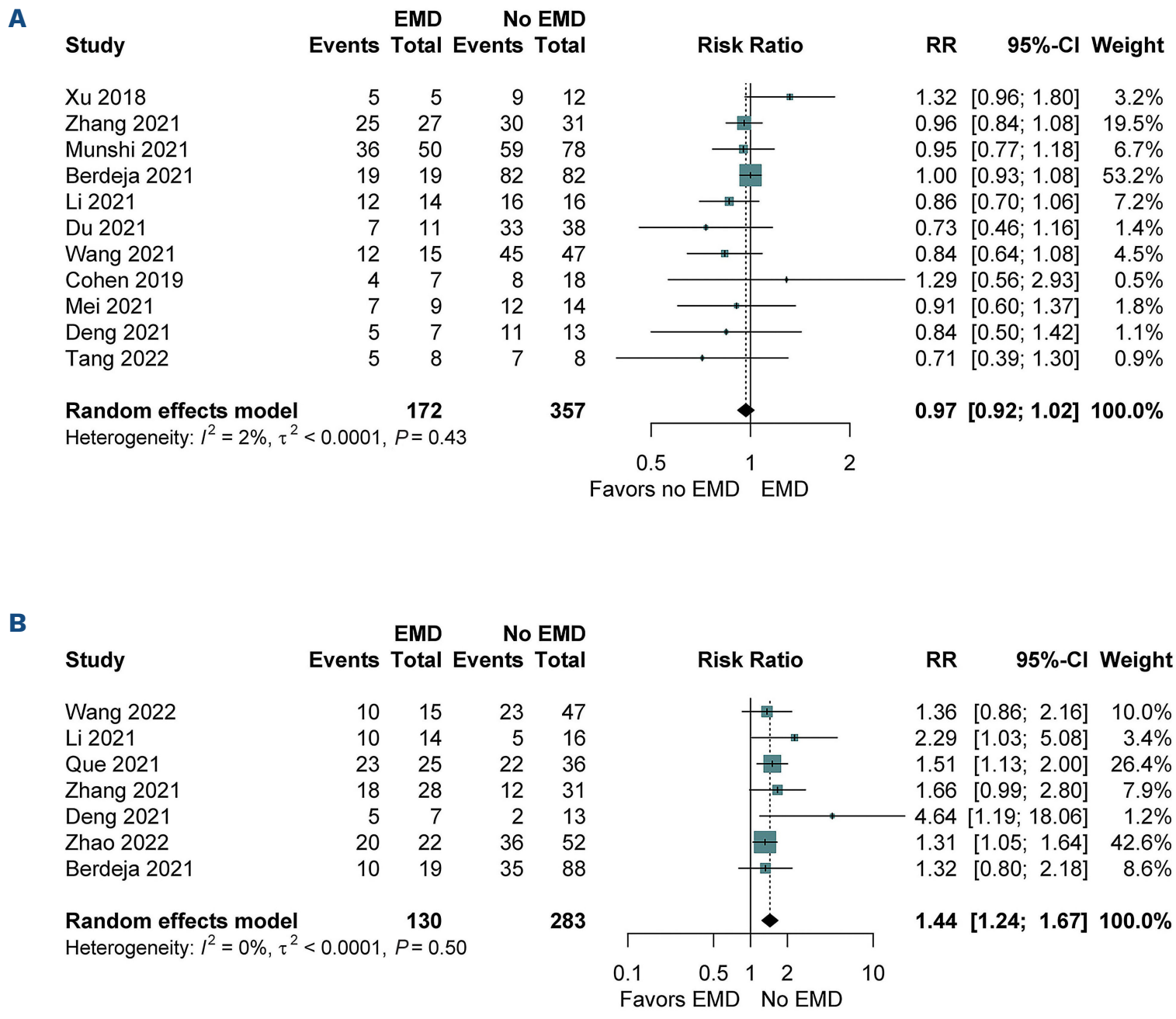

Figure 1. Results of the meta-analysis of outcomes of patients with or without extramedullary disease. (A) Overall response rate. (B) Progression-free survival. EMD: extramedullary discase; RR: risk ratio; CI: confidence interval.

Supplementary Figure S1). Heterogeneity is summarized in *Online Supplementary Table S2*; no heterogeneity was found for most outcomes.

There are currently several approved and ongoing T-cell redirection strategies in multiple myeloma (bispecific antibodies and CAR T-cell therapy) and understanding the immune microenvironment prior to treatment and at relapse or progression could provide insights into rational sequencing of certain treatments. For example, radiotherapy for accessible extramedullary manifestations represents a frequently used option for bridging in clinical practice. A recent study using bridging radiotherapy before CAR T-cell therapy showed that bridging appeared to be safe and feasible in relapsed/refractory patients.[14] This could be an option to reduce tumor burden during the currently long turnaround times required to provide the cell product, especially for patients who are in need of immediate symptomatic relief, who present with functional deficits, pathological fractures, or involvement of eyes and the central nervous system. Regarding competitive and new treatments with bispecific antibodies, response rates for the newly approved bispecific antibody teclistamab were lower in patients with extramedullary disease and R-ISS stage III disease, whereas high response rates were consistent across patients with high-risk cytogenetic abnormalities and those with penta-drug refractory disease.[15] Thus, together with results presented in our evidence synthesis, studies should evaluate the preferred treatment sequence or even a combination approach of bispecific antibody and CAR T cells for patients with high-risk cytogenetics and for those with extramedullary disease.[16] For high-risk patients, earlier treatment with CAR T cells and consolidation/maintenance after the CAR T-cell therapy showed promising results in a recent small study.[17] Whether this could overcome an initial poor prognosis and induce better immune surveillance should be investigated. In this regard, longitudinal assessment of changes of the immune microenvironment and timing of disease progression is urgently needed to understand the mechanisms of relapse and immune escape, especially in extramedullary disease.

In conclusion, high-risk cytogenetics were significantly associated with worse outcomes after CAR T-cell therapy for relapsed or refractory multiple myeloma. Although extramedullary disease showed promising initial responses, including decreases in measurable residual dis-

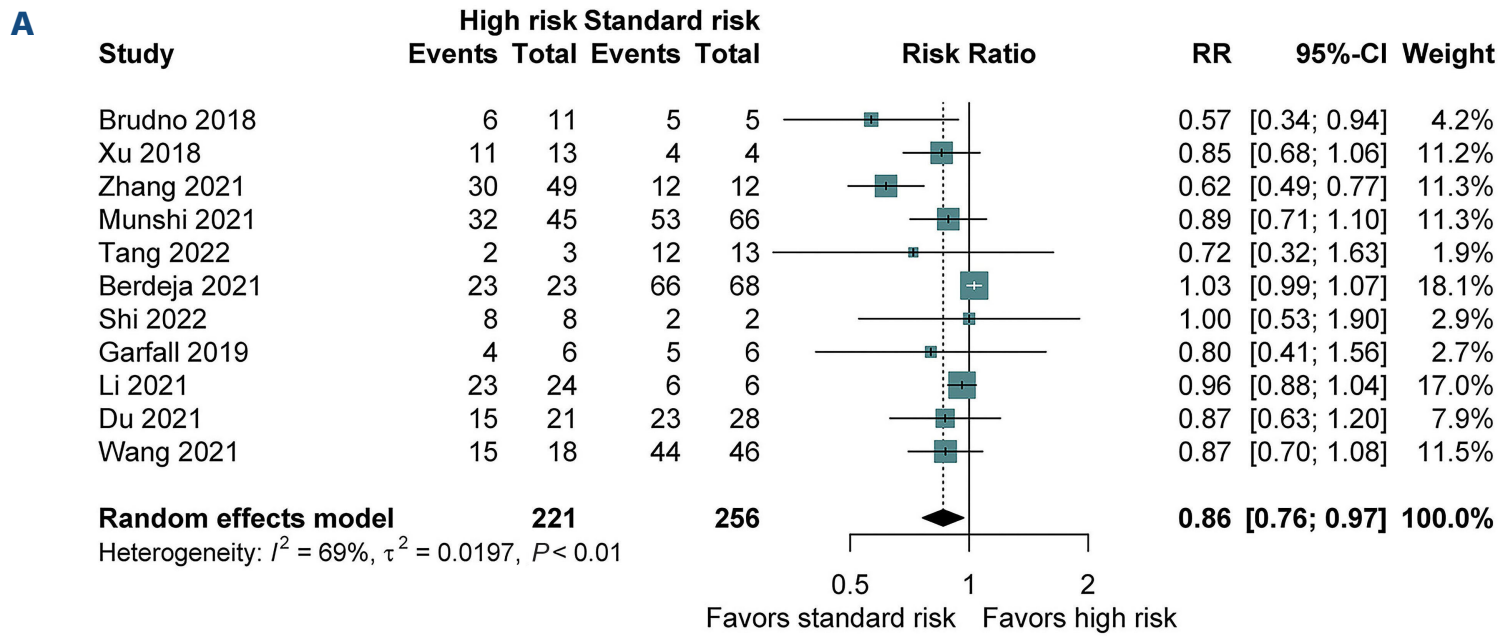

Figure 2. Results of the meta-analysis of outcomes for patients with high-risk versus standard-risk cytogenetics. (A) Overall response rate. (B) Progression-free survival. RR: risk ratio; CI: confidence interval.

ease, the risk of relapse and mortality was increased significantly, so the results should be interpreted with caution and underscore the need for future research into mechanisms of relapse, the design of innovative treatment sequencing studies, and careful follow-up of patients even after an initial response.

Authors

Nico Gagelmann, Francis A. Ayuk, Evgeny Klyuchnikov, Christine Wolschke, Susanna Carolina Berger and Nicolaus Kröger

Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Correspondence:
N. KRÖGER - nkroeger@uke.de

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Contributions

NG conceived the study design, searched literature, performed analyses, and wrote the first draft of the manuscript. NK searched the literature, performed analyses, interpreted results and wrote the first draft of the manuscript. FA, EG, CK and SCB interpreted results and wrote the manuscript. All authors approved the final version of the manuscript.

Data-sharing statement

Data can be made available if requested by e-mail to the corresponding author.

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