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None declared.

Prognostic Role of Cyclin D1 in Multiple Myeloma: A Systematic Review and Meta-analysis

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Review question / Objective: **Cyclin D1 has been identified as a proto-oncogene associated with uncontrolled proliferation of tumor cells. The relationship between CCND1 over-expression and prognosis of multiple myeloma(MM) patients remains controversial. This systematic review and meta-analysis aims to evaluate prognostic significance of cyclin D1 in determining the survival of MM patients.**
Condition being studied: **Multiple Myeloma. Obtained databases were from PubMed, Embase and Web of Science until February 2021. Two researchers independently extracted the data from predetermined included studies: the first author, mean age, year of publication, sex, sample size, country, detection methods, treatment methods, clinical stage, disease phase, follow-up period, prognostic indicators (OS, PFS, EFS, hazard ratios (HRs), and 95% confidence intervals (CIs)), and study design. The Stata software was used for the meta-analysis. HR was used as the effect, and OS and PFS/EFS were used to determine prognosis.Hazard ratio (HR) and 95% confidence interval (CI) were used to evaluate the relationship between cyclin D1 expression and overall survival (OS) and progression-free survival (PFS) in patients with MM.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 September 2021 and was last updated on 06 September 2021 (registration number INPLASY202190019).

INTRODUCTION

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METHODS

Participant or population: Cyclin D1-positive MM patients.

Intervention: Long-term follow up.

Comparator: Cyclin D1-negative MM patients.

Study designs to be included: Studies that designed a prospective or retrospective cohort study. Our study designs include data retrieval, inclusion and exclusion criteria, data extraction, literature quality evaluation and do meta-analysis using STATA software.

Eligibility criteria: (1) studies that detected cyclin D1 expression in myeloma cells via immunohistochemistry (IHC), polymerase chain reaction (PCR), or amplification of CCND1 gene by FISH; (2) studies that reported the relationship between expression of cyclin D1 and survival parameters, such as OS, PFS, and EFS; (3) studies that divided the expression of cyclin D1 into positive and negative groups; (4) studies that designed a prospective or retrospective cohort study; (5) studies in which the hazard ratio (HR) and 95% confidence interval (95%CI) for survival analysis appeared in the text or were extracted using the K-M curve.

Information sources: PubMed, Web of Science, and EMBASE.

Main outcome(s): There was a significant correlation between the prolongation of OS and increased expression of cyclin D1 in MM patients in the relapsed and refractory group (OS, HR=0.46, 95%CI: 0.24~0.90). Besides, patients with MM had longer overall survival in the bortezomib group(OS, HR=0.30, 95%CI: 0.11~0.82), whereas, MM patients with overexpression of CCND1 in the conventional chemotherapy group had poor prognosis (HR=2.19, 95%CI: 1.18~4.08). We also found that increased cyclin D1 expression correlated favorably with PFS in the autologous stem cell transplantation(ASCT) group (HR=0.45, 95%CI: 0.28~0.73). Conclusion MM patients overexpressing cyclin D1 treated with bortezomib or receiving ASCT are more likely to have better prognoses. In particular, the increased expression of cyclin D1 in the relapsed or refractory myeloma population seems to be associated with increased OS.

Quality assessment / Risk of bias analysis: The quality of selected studies was evaluated using the Newcastle-Ottawa scale (NOS). We graded the selected articles based on the choice of the study, comparability between groups, and determination of the results. Scoring ranged from 0 to 9, 0 being the minimum score, and 9 the maximum score. Studies with a NOS ≥ 6 were considered to be of high quality and low biased risk and were, therefore, included in the analysis. We used Egger's test and Begg's test in the Stata software to evaluate publication bias. The Begg's funnel chart was used to assess publication bias in the study, and the shape of the figure obtained was symmetrical. Egger's test and Begg's test indicated that the OS and PFS/EFS had no publication bias, which confirmed the robustness of our findings.

Strategy of data synthesis: The Stata software was used for the meta-analysis. HR was used as the effect, and the OS and PFS/EFS were used to determine prognosis. The Hazard ratio of the merger and a confidence interval of 95% CI were used to evaluate the relationship between the expression of cyclin D1 and prognosis. For articles that did not directly report the HR and 95% CI but provided Kaplan-Meier curves, we used EngaugeDigiizer4.1 to extract survival data from the Kmurm curve and then calculated the HR and 95%CI.

Subgroup analysis: We carried out a subgroup analysis of OS based on the disease phases and treatment. Overexpression of cyclin D1 in the relapsed and refractory group was associated with longer survival periods for MM patients (OS, HR=0.46, 95%CI: 0.24~0.90), and there was no significant heterogeneity in this group (I2=0.0%, p=0.523). In the newly diagnosed group, there was no significant association between the expression of cyclin D1 and prognosis (OS, HR=1.24, 95%CI: 0.73~2.09, I2=73.5%, p=0.000). According to the results of different groups based on the mode of treatment of the disease, high expression of cyclin D1 in the traditional chemotherapy group was linked to poor prognosis (OS, HR=2.19, 95%CI: 1.18~4.08), and the heterogeneity in this group was significantly smaller than before (I2=59%, p=0.062). Conversely, high expression of cyclin D1 in the bortezomib group was associated with better prognosis. Similarly, we carried out a subgroup analysis in the PFS/EFS group based on whether autologous stem cell transplantation was performed. We found that progression-free survival time of cyclin D1 positive MM patients in the autotransplantation group was longer than that of the cyclin D1 negative group (HR=0.45, 95%CI: 0.28~0.73), and there was no observable heterogeneity (I2=0%, p=0.825). The non-ASCT group had no reference meaning because of its significant degree of heterogeneity (HR=1.28, 95%CI: 0.43~3.83, I2=88.2%, p=0.000).

Sensitivity analysis: We conducted a sensitivity analysis, eliminating each of the included studies one by one, and merged HRs to check whether re-merged HRs and original changes were noticeably different. Our findings revealed that re-evaluated HRs were not different from the ones obtained from the first evaluation.

Country(ies) involved: China.

Keywords: Multiple myeloma, Prognosis, Bortezomib, Cyclin D1, Meta-analysis.

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YW Jiang designed the research study. YW Jiang, CL Zhang and L Lu collected data and performed data-analysis. YW Jiang drafted the manuscript and designed the figures. HY Liu, YJ Jiang and LM Hong contributed to the editing of the final manuscript. HM Huang and D Guo reviewed the manuscript.