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The 11th World Congress on
CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

The Adverse Therapeutic Outcomes and Efficacy Limitations Associated with CAR T-cell Therapy in the Treatment of Multiple Myeloma: A Systematic Review

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Introduction

Chimeric antigen receptor (CAR) T-cell therapy is a novel form of cancer treatment which has shown promising results in multiple myeloma (MM), especially in relapsed and refractory cases. While a significant proportions of patients with MM treated with CAR-T have achieved a good response, there is still opportunity for improvement, particularly in terms of response durability and treatment-associated toxicity. Indeed, there are some non-negligeable limitations to CAR-T cells therapeutic efficacy such as failure to achieve immunological memory and possible immune evasion. Furthermore, CAR T-cell therapy is associated with non-negligible toxicities which contribute to increased risk of morbidity and mortality.

In this systematic review, we examined the current evidence for CAR T-cell use in MM, focusing on limitations in efficacy and adverse therapeutic outcomes. Various databases were searched for studies on efficacy and adverse treatment outcomes following CAR T cell therapy in multiple myeloma up to January 2025. The efficacy outcomes of interest included the median progression-free survival (PFS), overall survival (OS) at 1-year and complete response rate (CR). An inventory of treatment-associated toxicities and adverse effects up to 1-year post-treatment was conducted, including their respective incidence rates.

Results

Sources and publication year	Number of patients	Median PFS in months	OS at 1-year	CR	Reported CAR T cell-associated toxicities
Raje et al. 2019	33	11.8	Not available	15 (45%)	-neutropenia (85%) -leucopoenia (58%) -anaemia (45%) -thrombocytopenia (45%) -cytokine release syndrome (70%) -neurotoxic effects (42%)
Mei et al. 2021	23	17.2	21 (93%)	12 (52%)	-cytokine release syndrome (87%) -neutropenia (96%) -leucopoenia (87%) -anaemia (43%)
Munshi et al. 2021	128	8.8	Not available	42 (33%)	-neutropenia (91%) -anaemia (70%) -thrombocytopenia (63%) -cytokine release syndrome (84%) -neurotoxic effects (18%)
Xu et al. 2019	17	Not available	14 (82%)	7 (41%)	-cytokine release syndrome (58%)
Rodriguez-Otero et al. 2023	254	13.3	Not available	99 (39%)	-cytokine release syndrome (88%) -neurotoxic effects (15%)
Li et al. 2022	54	16.4	Not available	11 (20%)	-haematological toxicities (51%) -cytokine release syndrome (100%)
Qu et al. 2022	31	Not available	25 (82%)	16 (52%)	-cytokine release syndrome (94%) -haematologic toxicities (100%) -neurological toxicity (93%)
Kfir-Erenfeld et. al. 2024	50	11.0	Not available	28 (56%)	-cytokine release syndrome (96%) -haematologic toxicities (98%) -neurological toxicity (6%)

Conclusion

After eligibility assessment, eight clinical trials were included, comprising a total of 590 participants. Complete response (CR) rates ranged from 33% to 56 % while overall survival (OS) after 1 year ranged from 82% to 93 %. The main forms of adverse therapeutic response included cytokine release syndrome (CRS) and haematological toxicities such as neutropenia, leucopenia, and thrombocytopenia. Haematological toxicities are speculated to result from the lymphodepleting regimen required before CAR T-cells infusion.(5, 8)

The results of this systematic analysis suggest that CAR-T cell therapy could potentially enhance CR rates compared to first and second-line treatment forms for multiple myeloma. However, the impact on survival is more ambiguous. The number of patients included in this systematic analysis is small, and many patients received concomitant forms of treatment, including chemotherapy, radiotherapy, and stem-cell transplant. This illustrates the need for well-designed randomised controlled trials to determine the true impact of CAR T therapy in multiple myeloma.

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Acknowledgement

The authors declare no conflict of interest.

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