CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY WITH MODERN MULTIPLE MYELOMA REGIMENS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting toxicity of proteasome inhibitor (PI)-based multiple myeloma therapy. Despite the shift from IV to SC bortezomib and newer agents (ixazomib, carfilzomib), no meta-analysis has compared CIPN across modern PI regimens incorporating SC dosing or CD38 monoclonal antibodies.

AIM

To compare pooled CIPN incidence across modern PI-based multiple myeloma regimens (SC vs IV bortezomib, ixazomib, carfilzomib) and evaluate the impact of CD38 monoclonal antibody coadministration on CIPN risk.

Secondary aim: identify predictors of CIPN risk via subgroup and meta-regression analyses of administration route, PI agent, dosing schedule, and cumulative drug exposure.

METHOD

Study design & population

- 25 RCTs (17,284 patients); adults with newly diagnosed or relapsed/refractory MM receiving PI-based regimens; CIPN graded per NCI-CTCAE.
- Primary outcomes: incidence of all-grade, grade ≥2, and grade ≥3 CIPN.
- Secondary outcomes: dose-modification rates, reversibility, and patient-reported neuropathy.
- Random-effects meta-analysis (DerSimonian–Laird); heterogeneity assessed via I^2 and Cochran Q.
- Subgroup/meta-regression by route, agent, schedule, CD38 mAb; GRADE applied.

CONCLUSIONS

SC bortezomib substantially reduces CIPN risk vs IV administration, though carfilzomib carries the lowest neuropathy burden among modern PIs. CD38 mAb coadministration may confer additional neuroprotective benefit — supporting individualized route/agent selection and standardized CIPN reporting in future MM trials.

RESULTS

Key findings

Overall pooled any-grade CIPN incidence was 38.4% (95% CI, 32.1–45.1; I^2=81%) across 25 RCTs (17,284 patients).

SC vs IV bortezomib (3 head-to-head RCTs): grade ≥2 CIPN RR 0.66 (95% CI, 0.49–0.89; P=0.006); dose modification 14.2% vs 27.4% (RR 0.52; P<0.001).

CD38 monoclonal antibody addition to SC bortezomib backbones reduced CIPN further (RR 0.81; 95% CI, 0.71–0.92; P=0.03).

Dose-response & certainty

Meta-regression: cumulative bortezomib exposure vs grade ≥2 CIPN, β=0.38% per mg/m² (P=0.001).

GRADE certainty was high for ixazomib/carfilzomib comparisons, moderate for SC vs IV bortezomib, and low to very low for reversibility outcomes.

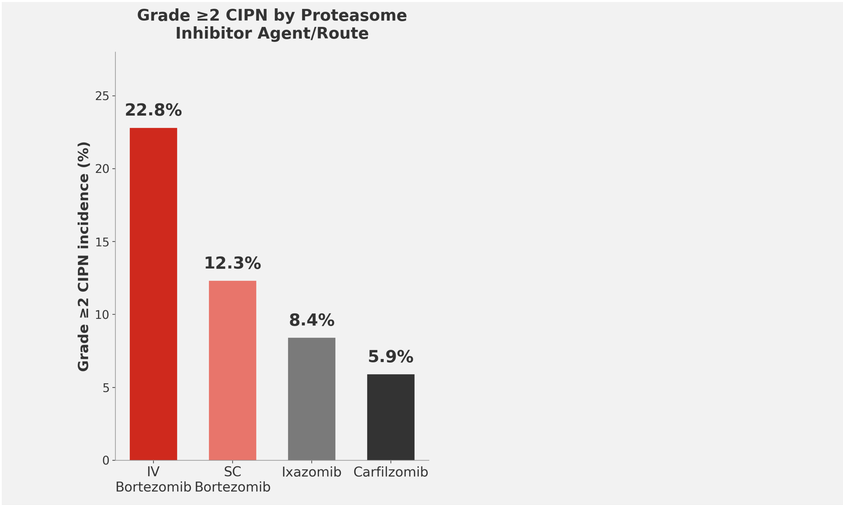

Figure. Pooled grade ≥2 CIPN incidence by proteasome inhibitor agent/route (RCT meta-analysis data).

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