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# Metronomic versus standard fixed dosing chemotherapy in human epidermal growth factor receptor-type 2-negative metastatic breast cancer: a reconstructed individual patient data meta-analysis

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**Objective:** To systematically evaluate and compare the efficacy and safety of metronomic chemotherapy versus standard fixed-dose chemotherapy in patients with human epidermal growth factor receptor-type 2 (HER2)-negative metastatic breast cancer through a reconstructed individual patient data meta-analysis. **Methods:** This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; under CRD42025645145). Randomized clinical trials comparing metronomic dosing with standard chemotherapy in HER2-negative metastatic breast cancer were identified through comprehensive searches on MEDLINE, Embase, and Cochrane databases. Primary outcomes included reconstructed individual patient data-based progression-free survival and overall survival. Secondary outcomes were objective response rate, disease control rate, and toxicity, assessed via pooled odds ratios (OR). **Results:** Four randomized clinical trials totaling 436 patients were analyzed. Compared to standard chemotherapy, metronomic chemotherapy significantly reduced progression-free survival (hazard ratio [HR] 1.22; 95% confidence interval [CI] 1.01–1.49;  $p < 0.05$ ) and overall survival (HR 1.38; 95%CI 1.08–1.76;  $p < 0.05$ ). There were no statistically significant differences in objective response rate (OR 1.26; 95%CI 0.77–2.08;  $p > 0.05$ ) and disease control rate (OR 0.77; 95%CI 0.50–1.17;  $p > 0.05$ ). Patients treated with metronomic chemotherapy experienced significantly fewer incidences of vomiting (OR 0.28; 95%CI 0.10–0.76;  $p < 0.05$ ) and alopecia (OR 0.16; 95%CI 0.08–0.31;  $p < 0.05$ ). No significant differences were observed for diarrhea, anemia, neutropenia, or hand-foot syndrome between groups. **Conclusion:** Metronomic chemotherapy is associated with a better toxicity profile, specifically reducing alopecia and vomiting, while maintaining similar response and disease control rates. However, standard fixed-dose chemotherapy provided superior progression-free and overall survival outcomes, thus remaining the recommended treatment standard. Clinicians should weigh the trade-off between quality of life and survival outcomes carefully in personalized treatment discussions.

**Keywords:** chemotherapy; breast cancer; meta-analysis.