Review: Adding cytotoxic drugs to an existing chemotherapy regimen increases tumor response rates and toxicity, but not survival in metastatic breast cancer

Jones D, Ghersi D, Wilcken N. **Addition of drug/s to a chemotherapy regimen for metastatic breast cancer.** Cochrane Database Syst Rev. 2006;(3):CD003368.

Clinical impact ratings: Oncology ★★★★★★☆

QUESTION

In women having first line chemotherapy for metastatic breast cancer, is the addition of ≥ 1 chemotherapy drug to an existing regimen of ≥ 2 drugs beneficial?

METHODS

Data sources: Cochrane Breast Cancer Group's specialized register (searched 3 August 2004, with an updated search 2 August 2005), reference lists, and related literature reviews.

Study selection and assessment

Randomized controlled trials (RCTs) that compared an existing chemotherapy regimen of ≥ 2 drugs compared with the same regimen and ≥ 1 additional drug in women receiving first-line chemotherapy for metastatic disease. 17 RCTs (n = 2674) met the selection criteria. Individual study quality was assessed based on generation of randomization, allocation concealment, comparability between groups at baseline, and inclusion of all randomized patients in the analysis. 16 RCTs were deemed of high quality.

Outcomes: Overall survival, progression-free survival, tumor response, and toxicity.

MAIN RESULTS

Overall survival and progression free-survival were unaffected by adding ≥ 1 or more drug (hazard ratio [HR] for death 1.0, 95% CI 0.9 to 1.1; P = 0.47; HR for progression 0.9, CI 0.8 to 1.1; P = 0.31). The addition of ≥ 1 drug led to higher rates of tumor response (Table) and toxicity: leucopenia (odds ratio [OR] 1.5, 95% CI 1.2 to 2.0), nausea and vomiting (OR 1.8, CI 1.3 to 2.5), and hair loss (OR 2.9, CI 1.8 to 4.4).

CONCLUSION

In women having first line chemotherapy for metastatic breast cancer, the addition of drugs to an existing regimen does not improve progression-free or overall survival, but does increase tumor response rates and toxicity.

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For correspondence: Ms. D. Ghersi, University of Sydney, Sydney, New South Wales, Australia. E-mail davina@ctc.usyd.edu.au.

The addition of 1 or more chemotherapy drugs to an existing regimen vs chemotherapy regimen alone for metastatic breast cancer*

Outcome	Number of) trials (n	Weighted event rates		RBI (95% CI)	NNT (CI)
		≥1 drug added to chemotherapy regimen	Chemotherapy regimen alone		
Tumor response	15 (2101)	44%	40%	11% (0 to 23)	25 (13 to ∞)

*Abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a fixed-effects model.

COMMENTARY

The Cochrane review by Jones and colleagues clearly shows that overall survival and progression-free survival are not improved by adding extra cytotoxic drugs to an existing regimen (≥ 2 drugs) in women having first-line chemotherapy for metastatic breast cancer. Toxicities such as leukopenia, nausea, vomiting, and alopecia were increased, as were rates of tumor shrinkage. More recent trials comparing 1- and 2-drug combinations had similar findings (1).

All trials in this review were published before 1992. This limits the direct applicability of the results to current practice. The trials did not include newer agents such as the taxanes, or targeted drugs such as trastuzumab and bevacizumab. More recent trials of newer agents have generally tested their addition to a single drug, and trials of that design were not eligible for this review. For example, the addition of capecitabine to docetaxel improved response rates, time to progression, and overall survival, but at the cost of increased toxicity (2). The addition of trastuzumab to paclitaxel also improved response rates, time to progression, and overall survival (3). Crossover to the alternate regimen makes it hard to find survival differences anyway, given most patients' strong desire for second-line treatment and willingness to put up with side effects (4).

Where does that leave us? The finding that adding ≥ 1 cytotoxic drug to an older combination (≥ 2 drugs) increases tumor responses and toxicity, but not survival, likely also applies to combinations of newer drugs, but probably not to single agents or the addition of targeted drugs. However, we don't give chemotherapy just to improve survival; sometimes combination treatment is given to quickly reduce tumor burden and symptoms. Matching the regimen to the tempo of the disease and avoiding toxicity both matter, as does a healthy dose of realism about end results. Data are needed about the effects of chemotherapy on outcomes that are important to patients, such as symptom relief, side effects, quality of life, and survival, to help guide its use. For newer and much more expensive drugs, data are also needed about their effects on health care costs in relation to incremental benefits.

James Khatcheressian, MD
Thomas J. Smith, MD
Virginia Commonwealth University
Richmond, Virginia, USA

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