Ixabepilone plus capecitabine with capecitabine alone for metastatic breast cancer

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CRD summary
The authors concluded that compared with capecitabine alone, ixabepilone plus capecitabine demonstrated a clinical activity with an acceptable safety profile in patients with locally-advanced breast cancer. There were concerns with trial quality and comparability, so caution is warranted when interpreting the authors’ conclusions.

Authors' objectives
To estimate the efficacy and safety of ixabepilone plus capecitabine compared with capecitabine alone in patients with locally advanced or metastatic breast cancer who are anthracycline and/or taxane resistant.

Searching
EMBASE, PubMed, the Cochrane Library, Chinese Journals Full-text Database, Chinese Biomedical Database, Chinese Scientific Journals full-text Database and CMA Digital Periodicals were searched to January 2009 for articles in any language. Search terms were reported. ClinicalTrials.gov, Google and other clinical trials registries were also searched. Reference lists of related articles and reviews were scanned. Published abstracts of the American Society of Clinical Oncology Annual Scientific Meeting and the San Antonio Breast Cancer Symposium were handsearched between 1995 and 2008.

Study selection
Randomised controlled trials (RCTs) that compared ixabepilone plus capecitabine with capecitabine alone, in patients with locally-advanced breast cancer who were anthracycline and/or taxane resistant, were eligible for inclusion. Patients were allowed to receive up to three prior chemotherapy regimens in any setting, with sequential neoadjuvant/adjuvant treatment counting as one treatment. Anthracycline and/or taxane resistance was defined as recurrence within six months in the adjuvant or neoadjuvant setting, or tumour progression during or within three months of treatment.

Relevant primary outcomes were overall survival, and time to progression. Relevant secondary outcomes were overall response rates and toxicity.

The included trials studied breast cancer patients who were resistant to anthracycline and a taxane, or pre-treated with anthracycline and a taxane. Included trials compared ixabepilone plus capecitabine with capecitabine alone.

Two authors independently undertook the selection process and disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Quality assessment was undertaken by two reviewers using the Cochrane Handbook 5 criteria, which assessed seven quality factors including randomisation, allocation concealment, blinding and loss to follow-up.

Data extraction
Two authors independently extracted the efficacy and safety data to calculate odds ratios (ORs) for dichotomous outcomes or weighted mean differences (WMDs) for continuous outcomes, together with 95% confidence intervals (CIs).

Methods of synthesis
The pooled odds ratios or weighted mean differences, together with 95% confidence intervals, were calculated using a fixed-effect or random-effects meta-analysis. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistic.

Results of the review
Two RCTs were included in the review (n=1,973 patients). The trials were deemed equally well-designed.
**Efficacy**: Compared with capecitabine alone, ixabepilone plus capecitabine had significantly greater overall survival (WMD 1.30, 95% CI 0.32 to 2.28; $I^2=100\%$), increased overall response rates (OR 2.42, 95% CI 1.45 to 4.02; $I^2=80\%$), and prolonged time to progression (WMD 1.65, 95% CI 1.36 to 1.94; $I^2=99\%$).

**Safety**: Compared with capecitabine alone, ixabepilone plus capecitabine had significantly greater rates of neutropenia (OR 8.85, 95% CI 5.24 to 12.96; $I^2=0\%$), myalgia (OR 6.49, 95% CI 1.45 to 28.97; $I^2=0\%$), and peripheral neuropathy (OR 31.85, 95% CI 6.24 to 162.61; $I^2=0\%$). There was no difference between capecitabine alone and ixabepilone plus capecitabine in terms of diarrhoea, stomatitis, febrile neutropenia, or hand-foot syndrome.

**Authors’ conclusions**
Compared with capecitabine alone, ixabepilone plus capecitabine demonstrated clinical activity with an acceptable safety profile in patients with locally-advanced breast cancer.

**CRD commentary**
Inclusion criteria for the review were clearly defined and several relevant databases were searched without language or publication status restrictions. Publication bias was not formally assessed and could not be ruled out. Two authors performed study selection, data extraction and quality assessment, which minimised the possibility of error and bias in the analysis.

No details of the quality assessment were presented and baseline trial characteristics were not available, which made verifying the quality and comparability of the two included trials difficult. Trials were combined using meta-analysis and heterogeneity was explored. However, there were extremely high levels of statistical heterogeneity in several of the analyses, which raised doubts as to the appropriateness of combining the trials through meta-analysis.

Given the concerns with trial quality and comparability, caution is warranted when interpreting the authors’ conclusions.

**Implications of the review for practice and research**
**Practice**: The authors stated that ixabepilone plus capecitabine seems to be a valid option for patients with anthracycline pre-treated/resistance and taxane resistant metastatic breast cancer.

**Research**: The authors did not state any implications for research.

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