Vinorelbine-related cardiac events: a meta-analysis of randomized clinical trials

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CRD summary
This review compared the risk of cardiac adverse reactions with vinorelbine in comparison with other chemotherapeutic agents. The authors concluded that approximately 1% of patients in clinical trials experience vinorelbine-related cardiac events, which is similar to other agents. The conclusion follows from the evidence, though restricting the review to randomised controlled trials means that relevant data might have been missed.

Authors' objectives
To quantify the incidence of cardiac adverse events with vinorelbine (VNR) in comparison with other chemotherapeutic agents.

Searching
MEDLINE (1987 to 2002), EBM Reviews, the Cochrane Library and Cancerlit (all from 1992 to 2002) and EMBASE (1988 to 2002) were searched for papers in English, German or French; the search terms were reported. The reference lists of review papers and relevant studies were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Trials with at least one arm with VNR alone or in combination with another drug, and a description of all groups of treatment, were eligible for inclusion. The included studies were of VNR alone, or as a combination, compared with cisplatinum, melphalan, etoposide, fluorouracil (5FU), vindesine (VDS), mitomycin, ifosfamide, epirubicin, carboplatinum, gemcitabine (GEM), doxorubicin, mitoxantrone and paclitaxel (PTX), either alone or in various combinations. The dose of VNR ranged from 20 to 30 mg/m² and the number of weeks between cycles of treatment ranged from 1 to 4.

Participants included in the review
Trials of patients with cancer were eligible for inclusion provided there was a complete description of the study population. The participants in the included studies were being treated for non-small-cell lung carcinoma (NSCLC) or advanced breast cancer (ABC). The mean age of the patients ranged from 54 to 74 years. Eleven studies excluded patients with pre-existing cardiac disease, four did not have such exclusion criteria, and it was unclear in another four.

Outcomes assessed in the review
Trials reporting the number and type of adverse events in each group were eligible for inclusion. The outcomes of interest were cardiac events, which were at least grade 3 toxicity according to World Health Organization toxicity criteria or similar standardised score, toxic deaths and cardiac deaths.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance.

Assessment of study quality
Studies were assessed on a scale from 0 (poor quality) to 26 (good quality), though the specific criteria used were not reported (see Other Publications of Related Interest). Two reviewers independently assessed the quality of the trials.
**Data extraction**
The authors did not state how the data were extracted. When no cardiac event or death was recorded for either arm of a trial, a value of 0.25 was used. The odds ratio (OR) and 95% confidence interval (CI) were estimated for cardiac events, cardiac deaths and toxic deaths for each study for VNR compared with all the other chemotherapeutic agents. The risk difference and 95% CI were also estimated. Patients who had received at least one course of treatment were included in the analysis. The authors of the included studies were asked to check the extracted data and provide any missing data.

**Methods of synthesis**
How were the studies combined?
The studies were pooled using the Mantel-Haenszel fixed-effect method.

How were differences between studies investigated?
In addition to pooling the studies separately for each of the three outcomes of interest, subgroup analyses were also conducted for the following: the outcome cardiac events for NSCLC and ABC carcinoma trials separately; trials with and without the exclusion of patients with cardiac disease; trials of VNR alone; trials where VNR was compared with cardiotoxic agents (5FU, anthracyclines, GEM, PTX and VDS); and VNR compared with VDS. The Breslow and Day chi-squared test was used to investigate statistical heterogeneity.

**Results of the review**
Nineteen RCTS (n=4,491) were included.

None of the trials were blinded and the method of randomisation was not always precisely described. The quality scores ranged from 13 to 22.

In total there were 58 cardiac events, 4 cardiac deaths and 63 toxic deaths across both groups. The incidence of cardiac events was 1.19% (95% CI: 1.17, 1.19) in the VNR group and 1.41% (95% CI: 0.90, 1.98) in the control group of other chemotherapeutic agents combined. There was no statistically significant difference between VNR and the other drugs in the risk of cardiac events (OR 0.92, 95% CI: 0.54, 1.55), cardiac death (OR 2.98, 95% CI: 0.31, 28.50), or toxic deaths (OR 1.39, 95% CI: 0.83, 2.34). There were no statistically significant differences between groups in the subgroup analyses.

There was no evidence of statistically significant heterogeneity.

**Authors’ conclusions**
Approximately 1% of treated patients in clinical trials experience VNR-related cardiac events. However, the risk of cardiac events with VNR seems to be similar to that of other chemotherapeutic agents used in the same conditions.

**CRD commentary**
The review addressed a clear research question using defined inclusion criteria. Several relevant databases were searched, although language restrictions were applied which might have resulted in the loss of relevant data. Apart from the processes used for data extraction, the review methodology was well described and included measures to avoid the introduction of error and bias. The quality of the included studies was assessed, though there was limited consideration of study quality in the analysis and the quality of the individual studies was not reported. The quality of recording adverse events in the primary studies tended to be variable and it would have been helpful to have had more information on this aspect of the studies. The statistical pooling seemed appropriate and subgroup analyses were conducted to investigate differences between the studies, though it was not explicitly stated that these had been specified a priori. The authors’ conclusions follow from the evidence presented; however, the inclusion of RCTs only in a review of adverse events may lead to a loss of relevant data.
Implications of the review for practice and research
The authors did not state any implications for practice or further research.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

MeSH
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.