Ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma: a clinical practice guideline

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CRD summary
This review concluded that the addition of ifosfamide to anthracycline-containing regimens might improve tumour response, but this did not translate into a survival benefit and treatment-related toxicities were increased. The authors' conclusions were in line with the evidence presented, but the limitations of the methodology suggest that these conclusions should be treated with caution.

Authors' objectives
To evaluate the safety and efficacy of combination chemotherapy regimens containing ifosfamide in patients with advanced soft tissue sarcoma.

Searching
The authors searched MEDLINE and EMBASE for articles from inception to July 2005 (updated to October 2007 by Verma, et al. 2008, see Other Publications of Related Interest) and the Cochrane Library (Issue 3, 2004). Search terms were reported and conference proceedings of the American Society for Clinical Oncology (1997 to 2005) and reference lists of relevant studies and reviews were also searched. Studies published in languages other than English were excluded.

Study selection
Randomised controlled trials (RCTs) comparing combination chemotherapy with or without ifosfamide, in adults with locally advanced or metastatic soft tissue sarcoma, were eligible for the review. Single-arm phase II trials of ifosfamide-containing regimens were included if they provided data that were not available from the RCTs. Trials had to report the time to progression or overall survival, in addition to the objective tumour response rate. Trials of dose-intensive chemotherapy with growth factor, or autologous bone marrow or stem cell transplant support and trials, in which patients received concurrent radiotherapy or surgery, were excluded.

Included RCTs compared regimens containing doxorubicin plus ifosfamide with doxorubicin alone or other doxorubicin-containing regimens. The phase II trials evaluated various regimens in patients with different histories of chemotherapy.

Trials were selected by one reviewer.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For the RCTs, the numbers of complete and partial responses in each group were used to calculate the relative risk and 95% confidence interval for tumour response. One-year mortality data were extracted from survival curves and used to calculate the relative risk for mortality. For the phase II trials, response rates were calculated.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks for response and mortality were derived by meta-analysis of the RCT data using a random-effects model. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. Response rates from phase II trials of ifosfamide plus an anthracycline in patients who had not previously received chemotherapy were pooled to calculate a weighted mean response rate. Response rates from individual trials were weighted by the inverse variance.
Results of the review
Three RCTs (1,402 participants), 16 phase II trials of ifosfamide with an anthracycline (857 participants), and seven phase II trials of ifosfamide in non-anthracycline combinations (348 participants) were included.

In the RCTs, ifosfamide-containing regimens significantly improved tumour response compared with those that did not contain ifosfamide (RR 1.52, 95% CI 1.11 to 2.08), but there was no difference in one-year mortality (RR 0.98, 95% CI 0.85 to 1.13). Statistical heterogeneity was not significant. The pooled response rate in nine phase II trials of ifosfamide plus an anthracycline in patients who had not previously received chemotherapy was 35% and the median survival ranged from eight to 16 months.

Higher rates of adverse events, particularly myelosuppression, were observed in patients who received ifosfamide-containing regimens. In the RCTs, more deaths due to toxicity were reported with the ifosfamide-containing regimens.

Authors' conclusions
The addition of ifosfamide to anthracycline-containing regimens might improve tumour response, but this did not translate into a survival benefit. Treatment-related toxicities were increased by the addition of ifosfamide.

CRD commentary
The review had clear inclusion criteria. Uncontrolled studies were included alongside RCTs, but the authors provided a justification for this and the review conclusions were mainly based on the evidence from RCTs. The authors searched a number of databases and made some efforts to locate unpublished trials. Only trials in English were included, so the review could have omitted relevant trials published in other languages. Trials were selected by one reviewer, which means that the process could have been affected by reviewer error or bias. The methods of data extraction were not reported. Relevant details of the included trials were reported, but an assessment of their validity was not, which means that their reliability and that of the synthesis derived from them are uncertain. The included RCTs were pooled by meta-analysis and the statistical heterogeneity was investigated.

The authors' conclusions were in line with the evidence presented, but the limitations of the methodology, particularly the lack of validity assessment, suggest that these conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that the addition of ifosfamide to doxorubicin-containing chemotherapy regimens was not recommended.

Research: The authors stated that future research should investigate the use of ifosfamide as part of a neo-adjuvant regimen for patients with inoperable locally advanced soft tissue sarcoma and future trials should evaluate the effects on quality of life.

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Record Status
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.