A systematic review of the accuracy and utility of early markers of ifosfamide-induced proximal tubulopathy in survivors of childhood cancers

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CRD summary
This review evaluated the accuracy and clinical utility of early markers of ifosfamide-induced proximal renal tubulopathy in survivors of childhood cancer. The authors concluded that there was a lack of good quality studies evaluating this subject. The quality of included studies was not assessed, but this conclusion appears to be reliable.

Authors' objectives
To evaluate the accuracy and clinical utility of early markers of ifosfamide-induced proximal renal tubulopathy in survivors of childhood cancer.

Searching
The Cochrane Library, MEDLINE, and EMBASE were searched and search terms were reported. Reference lists of relevant studies were checked and the Science Citation Index was used to identify additional studies. Studies published in English, Arabic, or German were eligible.

Study selection
Studies on paediatric cancer patients were eligible for inclusion if they assessed the accuracy of blood or urine tests as early markers of ifosfamide-induced proximal renal tubulopathy. Identified studies evaluated urinary beta 2-microglobulin levels and quantitative aminoaciduria. Proximal renal tubulopathy was defined as the long-term requirement of electrolyte and bicarbonate supplementation with or without the development of Fanconi syndrome.

The age of patients in the included studies ranged from six months to 24 years. The ifosfamide dose ranged from 2g to 126g per m$^2$. Patients in the included studies had neuroblastoma, sarcoidosis, or other types of cancer.

Two reviewers selected studies for inclusion, with disagreements settled by discussion among all four authors.

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

Data extraction
Data were extracted or calculated in order to report percentages for sensitivity and specificity and their 95% confidence intervals (CIs). Two independent reviewers extracted this data.

Methods of synthesis
A narrative synthesis was undertaken. Study differences were evident from the data in tables.

Results of the review
Four studies (n=138 patients) were included in the review. Sample sizes ranged from 15 to 75. The duration of follow-up ranged from 2 to 71 months. The overall prevalence of clinically significant chronic tubulopathy varied from 6 to 46%.

Urinary beta 2 microglobulin: This was assessed in two studies (n=48). One study (n=23) defined abnormal urinary beta 2 microglobulin as ≥10mg/mmol of creatinine. All three patients who had elevated levels developed chronic proximal tubulopathy, whereas none of the remaining 20 patients with lower levels of beta 2 microglobulin developed the disease (sensitivity 100%, 95% CI 29 to 100; specificity 100%, 95% CI 84 to 100). The other study (n=25) defined abnormal urinary beta 2 microglobulin levels as absolute loss of ≥ 2mg/L. Two out of the four patients with elevated urinary beta 2 microglobulin levels developed chronic proximal tubulopathy, whereas no other patients developed the disease over the 18-month follow-up period (sensitivity 100%, 95% CI 40 to 100; specificity 82%, 95% CI 74 to 98).
Aminoaciduria: This was assessed in three studies (n=113). The definition of aminoaciduria varied between the studies. The tests had a sensitivity ranging from 33% to 92% and specificity ranging from 84% to 90%. The confidence intervals around these estimates were wide.

Authors' conclusions
There was lack of good quality studies on the usefulness of early markers in identifying patients at higher risk of development of ifosfamide-induced proximal renal tubulopathy.

CRD commentary
This review addressed a clear question and was supported by detailed inclusion criteria for aspects of study design, participants, interventions, and outcomes. The search strategy appeared to include relevant sources and covered publications in three languages. The search period was not reported. Quality assessment of studies was not undertaken. Adequate details of the included studies were provided, indicating the existence of substantial variation that necessitated a narrative synthesis of the results. The review process was conducted with sufficient measures to minimise error and bias throughout.

Overall, this was a well-conducted review and based on the evidence provided the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated the need for studies with long term follow-up evaluating the early markers of proximal tubular nephropathy in childhood cancer patients treated with ifosfamide-based regimens.

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