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Title **A Systematic Review and Evaluation of the Use of Tumor Markers in Pediatric Oncology: Ewing's Sarcoma and Neuroblastoma**

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Aim

1. To perform the first systematic review of studies of tumor markers in the Ewing's sarcoma family of tumors (ESFT) and neuroblastomas to identify measures of potential clinical value for the clinical areas of screening, diagnosis, prognosis, and monitoring; the review focuses particularly on the role of markers for defining prognosis.
2. To facilitate development of future research strategies, including improving scientific reporting and specifying deficiencies in the literature.

Conclusions and results

Many papers were identified. For ESFT, the following were found to be potentially important prognostic tools and associated with a worse outcome: high levels of serum lactate dehydrogenase, lack of S-100 protein expression in the tumor, and lack of expression of the EWS-FLI type 1 fusion transcript in the tumor. For neuroblastomas, the following were found to be potentially important tools and associated with a worse outcome: amplification of the MYC-N gene; expression of diploid cells (a DNA index of 1) in the tumor; high expression of neurone-specific enolase in the tumor at diagnosis; high serum levels of lactate dehydrogenase and/or ferritin; high multidrug resistance gene-product expression in the tumor; gain of chromosome 17q; deletion of chromosome 1p; low tumor expression of CD44 and/or TrkA; and a low urinary VMA:HVA ratio.

Recommendations

The evidence is insufficient to judge the clinical role of tumor markers in treating the two childhood malignancies studied. Many markers have been studied, but most studies are so poorly designed and reported that strong clinical conclusions cannot be made from this systematic review. However, the authors identified markers that showed possible prognostic importance. Rapid development of genetic epidemiology may soon provide new genetic markers and sequences that supersede many of the markers identified as important.

Methods

MEDLINE, EMBASE, and CancerLit were searched from 1966 to February 2000. Papers had to provide a quantitative result or tabulated individual patient data (IPD) evaluating the use of a tumor marker in ESFT or neuroblastomas, based on primary research data from humans relevant to screening, diagnosis, prognosis, or monitoring. Meta-analysis was performed for tumor markers on which 3 or more papers provided data. For meta-analysis of prognostic data, estimates of the natural log of the hazard ratio and its variance were sought. If direct estimates were not reported, indirect estimates or IPD were used.

Further research/reviews required

Nine key issues for further research are discussed. The review demonstrates the need for better reporting and design of studies. The authors present guidelines on how to report the results of prognostic marker studies. Primary studies of prognostic markers need to make available their individual patient data, as this is the most viable way to facilitate evidence based reviews, and thus would allow evidence based conclusions and policy decisions to be made to improve patient care.

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