Tumour markers in paediatric oncology

A systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma

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Executive summary

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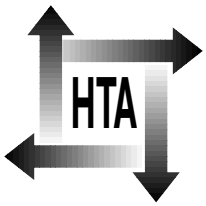

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Executive summary

Objectives

- To perform the first systematic review of studies of tumour markers in the Ewing's sarcoma family of tumours (ESFT) and in neuroblastomas in order 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.
- To facilitate the development of future research strategies, including improvement of the standard of scientific reporting and specification of deficiencies in the literature.

Methods

The databases MEDLINE, EMBASE and CANCERLIT were searched iteratively to identify the relevant literature from 1966 to February 2000. Sets of keywords relating to **tumour markers**, **ESFT** or **neuroblastoma**, and **clinical use** were developed; papers were identified if they contained a word from each of these sets.

To be included, papers had to provide a quantitative result or tabulated individual patient data (IPD) evaluating the use of a tumour marker in ESFT or neuroblastomas, based on primary research data from humans relevant to screening, diagnosis, prognosis or monitoring. Review articles and those reporting only laboratory work, methodologies for identifying new markers, or results from animal studies were thus excluded. Histological characteristics of tumours were not included in the markers reviewed.

From papers classified as 'relevant', information was extracted on the tumour marker used, the clinical area of application, the age range of patients, stage of disease, whether the outcome was overall survival (OS) or disease-free survival (DFS), and the cut-off level of the marker.

Meta-analysis was performed, where possible, for those tumour markers on which three or more papers provided data. For the meta-analysis of prognostic data, estimates of the natural log of the hazard ratio ($\log_e$(HR)) and its variance were sought. Where direct estimates were not reported, indirect estimation or IPD were used to obtain an unadjusted, or if necessary, an adjusted estimate.

The 'relevant' papers were also screened for any results from economic or psychosocial evaluations of the clinical use of tumour markers in ESFT or neuroblastomas.

Results

Tumours of the Ewing's sarcoma family

Eighty-four 'relevant' papers were identified which studied 70 different markers. Eighty-four papers related to diagnosis, 45 to prognosis and five to monitoring, but none to screening. Meta-analysis of the data from the diagnosis or monitoring papers was not possible because of the poor quality and reporting of data.

Meta-analysis of prognostic papers was possible but hindered by the extremely poor presentation of survival analyses. Of 132 attempts to obtain estimates of $\log_e$(HR) and its variance, only 83 proved successful. Only six of these 83 HRs were provided directly in a paper, ten had to be calculated indirectly and the remaining 67 were calculated using the IPD available.

High levels of serum lactate dehydrogenase and lack of S-100 protein expression in the tumour were significantly associated with a worse prognosis and an increased risk of death or disease recurrence/death. Expression of the EWS–FLI type 1 fusion transcript in tumours from patients with localised disease was associated with a more favourable outcome and reduced risk of disease recurrence/death, compared with expression of other EWS–ETS fusion transcripts. However, these results must be treated with caution given the poor reporting problems identified.

No studies reported an economic or psychosocial evaluation, which perhaps reflects the lack of certainty about which markers show enough clinical effectiveness and importance to warrant subsequent economic/psychosocial studies.

Neuroblastomas

Four hundred and twenty-eight 'relevant' papers were identified, which studied 195 different markers. The screening results demonstrated uncertainty as to whether population-based screening for neuroblastomas is clinically effective and cost-effective, and, if so, what is the optimal age at which to screen, and also the optimal screening strategy, that is, single stage or multi-stage. No meta-analysis of the data from the diagnosis or monitoring papers was performed because of the large degree of heterogeneity and inadequacy in reporting.

Thirteen tumour markers were studied in depth for their prognostic value. Of 575 occasions where levels of one of these markers were related to survival by summary statistics or IPD, only 204 successful estimates of $\log_e$(HR) and its variance were obtained because of inadequate, incomplete and inconsistent reporting. IPD were used to obtain 41 of these estimates.

Development of clinically meaningful results was difficult because of heterogeneity in the stage of disease, age of patients, marker cut-off level, outcome observed (OS or DFS), type of estimate (unadjusted or adjusted), and adjustment factors. Publication bias was also observed. Despite these problems, the following were found to be significantly associated with patients experiencing a worse outcome: amplification of the *MYC-N* gene; expression of diploid cells (a DNA index of 1) in the tumour; high expression of neurone-specific enolase in the tumour at diagnosis; high serum levels of lactate dehydrogenase and/or ferritin; high multidrug resistance gene-product expression in the tumour; deletion of chromosome 1p; low tumour expression of CD44 and/or TrkA; and a low urinary VMA:HVA ratio. Studies published since the start of our review indicate that chromosome 17q is an important prognostic marker, and so in retrospect we also reviewed the prognostic literature for this marker; gain of chromosome 17q was found to be associated with a worse OS and DFS.

No papers reported a psychosocial or an economic evaluation; two papers reported cost data in relation to screening but the information was of limited value. Once a tumour marker has been identified as clinically effective, the decision to use the marker in practice (e.g. for screening or monitoring) also involves the cost of its implementation and the psychological impact it has on patients; hence, it was disappointing to identify such large gaps in the literature, but this perhaps reflects the uncertainty as to which markers are indeed clinically effective.

Conclusions

Implications for clinicians

- There is currently insufficient evidence to judge the clinical role of tumour markers in the treatment of the two childhood malignancies we studied. A large number of markers have been studied in the literature but the majority of studies are so poorly designed and reported that strong clinical conclusions cannot be made from this systematic review. However, we did manage to identify markers that showed possible prognostic importance.
- 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 tumour, and lack of expression of the EWS–FLI type 1 fusion transcript in the tumour.
- 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 tumour; high expression of neurone-specific enolase in the tumour at diagnosis; high serum levels of lactate dehydrogenase and/or ferritin; high multidrug resistance gene-product expression in the tumour; gain of chromosome 17q; deletion of chromosome 1p; low tumour expression of CD44 and/or TrkA; and a low urinary VMA:HVA ratio.
- Clinical interpretation of the above findings is very difficult because of poor and heterogeneous reporting in the literature identified. The benefits of using these prognostic markers in practice needs to be properly studied in large, multicentre studies.
- The current rapid development of genetic epidemiology may quickly provide new genetic markers and genetic sequences that supersede many of the markers we have identified as important.

Implications for those conducting and reporting primary studies

- **Reporting of results needs to be improved**. Results of all the marker analyses should be presented – both significant and non-significant results – further details are described in the main report. In particular, individual patient data should be made available, including ▶

exact initial marker level, method of measurement, time of disease recurrence, follow-up time, final disease status and treatment received for all tumour markers considered.

- **A move toward evidence-based use of tumour markers is needed**. Investigation of potentially new and clinically better markers should not be at the expense of establishing how existing markers can be most effectively used in practice. For this, **collaboration of research groups is required** to assess clinical application of markers in studies with much greater patient numbers and to achieve consistency in reporting, for example for cut-off level, outcome assessed (OS or DFS), and adjustment factors.
- **Central repositories for IPD required**. To help collate and manage IPD, central repositories are necessary for each disease area.
- **Future genetic studies to follow our guidelines of reporting and facilitate access to IPD**. With the growth in genetic epidemiology potentially leading to identification of genetic markers that could supersede the important markers currently in use, it is very important that those studies are reported properly and make available IPD. Again, central repositories are required to collate and manage such IPD.
- Large, multicentre well-controlled studies are required to assess levels of multiple markers.
- **Economic and psychosocial evaluation of markers is required**. Once a marker has been identified as clinically effective, the decision to use the marker in practice (e.g. for screening or monitoring) also involves the cost of its implementation and the psychological impact it has on patients. Hence, economic and psychosocial evaluations are necessary.

Implications for meta-analysts

- Sensitivity and multifactorial analyses are needed to explore and adjust for effects of different cut-offs, stages of disease, outcomes (OS or DFS), ages and adjustment factors.
- Results from IPD (the 'gold standard' in the reporting of data) need to be compared with those from indirect methods to assess the reliability, validity and bias of use of the latter.

Implications for those conducting future systematic reviews

- Those considering future systematic reviews of tumour markers should seek to obtain individual patient data, as this is likely to be the most productive approach.

Publication

Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al.* A systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma. *Health Technol Assess* 2003;**7**(5).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme continues to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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