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Letter

Where to next with extracranial rhabdoid tumours in children

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Rhabdoid tumours are rare, highly aggressive and frequently lethal tumours of childhood. Renal rhabdoid tumour was first recognised as a separate pathological entity in the early 1980s [1]. Atypical teratoid/rhabdoid tumour (AT/RT) of the central nervous system (CNS) is well defined [2] and rhabdoid tumours have been reported widely at many other anatomical sites [3,4]. Although there are many reports describing their lethal outcome [4,5] there are few published series describing their management in a consistent manner on national or international protocols [5,3]. This is mainly due to their rarity. Data from the National Registry of Childhood Tumours (NRCT) for 1987—1999 give annual incidence rates in the United Kingdom (UK) of 0.24 per million children under 15 years for renal and 0.15 per million for extracranial extrarenal rhabdoid tumours. Incidence of AT/RT was 0.11 per million, but this may well be an underestimate [2]. Recently, there have been reports of survivors, even when there has been metastatic disease, with the use of more intensive chemotherapy regimes including doxorubicin [6,7].

There has been considerable debate over whether extrarenal rhabdoid tumour represents the same entity as rhabdoid tumour of the kidney. However, recent progress in analysis of their molecular biology has shown that they share a common genetic defect, namely deletion or mutation of the *hSNF5/INI1* gene on chromosome 22q [8]. In two subsequent studies of substantial numbers of tumours, mutation of the *hSNF15/INI1* gene was found in 25 of 29 extrarenal rhabdoid tumours and in 51 of 76 renal rhabdoid tumours [9,10]. It is less clear whether all non-CNS extrarenal malignant rhabdoid tumours have the same histogenetic origin as their renal counterparts [11,12,13], as some of these tumours may be considered to be undifferentiated sarcomas or carcinomas with "rhabdoid features". In these cases, documention of a *hSNF5/INI1* mutation may be helpful in diagnosing the true malignant rhabdoid tumours. Underlying *hSNF/INI1* gene mutations may also explain the association of renal rhabdoid tumours with brain tumours. These brain tumours are usually located in the midline cerebellum and may be of diverse histological composition, not always conforming to the definition of AT/RT. However, again most of these CNS rhabdoids, whether they occur in association with extracranial primary tumours or not, carry mutations in *hSNF5/INI1* (46 of 61 cases in two recent studies) [9,10]. There is some suggestion of a genotype-phenotype correlation, with exon 9 mutations reported almost exclusively in CNS rhabdoids in one study [9] and homozygous deletions being commoner in extracranial rhabdoid tumours in the other [10]. Germline predisposing mutations in *hSNF5/INI1* are found in children with rhabdoid tumours, particularly those with combined CNS and extracranial rhabdoid tumours [9].

Mutation of the *hSNF5/INI1* gene appears to be confined to rhabdoid tumours, particularly when in extracranial sites. Analysis of other non-CNS embryonal tumours types, even those that demonstrate allele loss for the chromosome 22q region spanning the *hSNF/*

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INI1 gene locus, has failed to identify any such mutations [10]. However, a small proportion of other embryonal CNS tumours, including some cases diagnosed histologically as choroid plexus carcinoma or cellular primitive neuroectodermal tumour (PNET), do carry *hSNF5/INI1* mutations.

Progress in understanding the biology of rhabdoid tumours therefore supports a common therapeutic approach, at least to extracranial rhabdoid tumours, where the added complexities of the blood-brain barrier do not apply. We have reviewed the outcome of 21 (11 male) patients with renal rhabdoid tumours treated in the UK between 1987 and 1999 on two consecutive national Wilms' tumour protocols (UKW2 and UKW3). The median age at diagnosis was 1.7 years (range 0–5.4 years). Fourteen of the 21 patients had localised tumours treated by initial nephrectomy (2 stage I, 3 stage II, 9 stage III). Of the remaining 7 patients with Stage IV disease, 3 patients had initial nephrectomy, 3 patients had nephrectomy after initial chemotherapy and response, and one patient received biopsy only as they progressed and died before the planned nephrectomy. In that time period, there were a further 14 patients registered in the NRCT in the UK with renal rhabdoid tumours, but as they were not treated on trials, their pathology has not been reviewed centrally and they have therefore been excluded from this review.

The chemotherapy regimen recommended for renal rhabdoids, regardless of tumour stage, in both the UKW2 and UKW3 trials consisted of intravenous (i.v.) vincristine 1.5 mg/m^2—weekly×11 then every 3 weeks, together with actinomycin D 1.5 mg/m^2 and doxorubicin 30 mg/m^2 given at 3 weekly intervals for a total of 1 year. Total planned doses of doxorubicin were 360 mg/m^2. Patients with abdominal stage III tumours were also recommended to receive 30 Gy radiotherapy of the flank.

The 5-year survival was 35% (standard error 9%), all deaths occurred within 13 months of diagnosis. Both Stage I patients survived, all three Stage II patients died, four of the nine Stage III patients survived and only one of the Stage IV patients survived. Two of the four Stage III patients who survived had had local radiotherapy.

During the same time period, there were 22 children notified to the NRCT with extracranial, extrarenal rhabdoid tumours. Three-year survival was 9% (standard error 6%), even lower than for renal rhabdoid tumours. The diagnoses of these patients have not been subject to central review, but it seems likely from the extremely low survival rate that a diagnosis of rhabdoid tumour, whether made locally or after review, is still associated with a very poor prognosis.

The case reports of Wagner [7] and Waldron [6], plus these data, emphasise the need to tackle this difficult tumour in a more consistent manner. This requires collection of more epidemiological and biological data, as well as international collaboration for the development of treatment protocols. With this in mind, at a recent separate meeting of the SIOP Wilms' Committee and the newly formed European Soft Tissue Sarcoma Group, it was decided to co-ordinate existing knowledge of treatment and outcome of renal and extrarenal rhabdoid tumours in several European countries (contact Dr. B Brennan—email: bernadette.brennan@cmmc.nhs.uk). This will provide a basis for discussing the incorporation of phase I/II window studies of novel agents into the treatment of patients with residual disease after surgery or stage IV tumours, to identify active drugs in this tumour type. An option under discussion, proposed by the Children's Oncology Group, is to utilise a protracted schedule of irinotecan that has shown activity in xenografts (Jeff Dome, St. Jude Children's Research Hospital, Memphis, TN, USA, data not shown).

Given the rarity of rhabdoid tumours, progress will only be made by international collaboration. Through this letter, we would like to inform European Paediatric Oncologists of a number of interesting proposals and to encourage them to become involved in the dialogue/initiative aimed at developing an international trial including this rare tumour type.

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