Extracranial rhabdoid tumours: what we have learned so far and future directions

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Extracranial rhabdoid tumours are rare, and often occur in infants. Although the kidney is the most common site, they can occur anywhere in the body. Most contain a biallelic inactivating mutation in *SMARCB1*, which is part of the chromatin remodelling complex SWI/SNF, and functions as a classic tumour suppressor gene. Despite multimodal therapy, outcome in rhabdoid tumours remains poor with only 31% of patients surviving to 1 year. The young age of patients limits use of radiotherapy, which, along with age, is an important prognostic factor. Because the tumours are rare, no standard therapeutic pathway exists, and no randomised trials have examined the role of new therapeutic approaches. Improved understanding of the biology and role of *SMARCB1* has enabled identification of new targets for small molecule inhibitors to combine with chemotherapy backbones that we might establish from the current EpSSG and COG studies.

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Introduction

Beckwith and colleagues[1] first described extracranial rhabdoid tumours as a distinct pathological entity in 1978. In 1981, Haas and colleagues[2] recognised rhabdoid tumour of the kidney as a separate tumour rather than a variant of Wilms', and introduced the term rhabdoid because of the tumour cells' close histological resemblance to rhabdomyoblasts. Results of subsequent studies have not confirmed a myogenic origin of the tumour cells, but the term is still used.[2] In 1989, Weeks and colleagues[3] published 111 cases of rhabdoid tumour of the kidneys from the National Wilms' Tumour Study (NWTS) pathology centre—the tumour was then recognised as a distinct entity. The *SMARCB1*-deficient group of tumours is increasing in size. Within this family, rhabdoid tumours have specific clinical and histological features, that distinguish them from other *SMARCB1*-deficient tumours, and therefore make them of specific interest. They usually contain the classic rhabdoid cell with vesicular and eccentrically placed nuclei containing a single prominent nucleolus, and eosinophilic inclusions in the cytoplasm.

Incidence and epidemiology

106 children younger than 15 years were diagnosed with extracranial rhabdoid tumours in the UK between 1993 and 2010.[4] The age-standardised annual incidence was 0·6 per 1 million children. Rhabdoid tumours occur predominantly in infants younger than 1 year. Incidence was five per million in the first year of life and decreased to 0·6 per million at age 1–4 years, 0·1 at age 5–9 years, and 0·04 at age 10–14 years. 55 of the cases were boys and 51 were girls—a sex ratio of 1·1:1. The table shows the distribution of cases by age and primary site. The most common site was the kidney, accounting for 48% of cases. 14% of tumours arose in the head and neck, 13% in the liver, and 25% in a wide range of other sites in the trunk and arms, but no cases of rhabdoid tumour of the lower limbs were recorded. The proportions of rhabdoid tumours at different sites that were diagnosed in infants (aged 0–12 months) were 79% for liver, 65% for kidney, 47% for head and neck, and 54% for other sites. Rhabdoid tumours accounted for 18% of all renal cancers in infants, 9% of hepatic cancers, and 14% of soft tissue tumours. In children aged 1–14 years rhabdoid tumours accounted for less than 2% of each of these categories.

Population-based data for rhabdoid tumours in other countries or in adolescents and adults are scarce. The estimated age-standardised annual incidence of rhabdoid tumours of the kidney across 19 European countries in 1988–97 was 0·1 per million and the rate in the first year of life was 1·0 per million.[5] These rates are substantially lower than the UK data and probably indicate under-recording rather than geographical or temporal variations in incidence. In the USA Surveillance Epidemiology and End Results (SEER) registries between 1973 and 2006, rhabdoid tumours accounted for 14% of all soft-tissue sarcomas diagnosed in the first year of life[6]—the same proportion as in the UK data. In the SEER data, 65 (60%) of 109 extrarenal, extracranial rhabdoid tumours were in people aged 20 years and older.[7] Malignant rhabdoid tumours in adults are less well described and hence the adult tumours included in the SEER data might not be the classical rhabdoid tumours, but rather other tumours with a rhabdoid phenotype. Inactivation of both copies of the *SMARCB1* gene leads to loss of protein expression in the nucleus, which can be detected by a SMARCB1 immunohistochemistry assay, most frequently using the BAF47

	Age at diagnosis				Total
	0 years	1 years	2–4 years	5–14 years	
Kidney	33	8	8	2	51
Liver	11	3	0	0	14
Head and neck	7	0	6	2	15
Other	14	4	3	5	26*
Total	65	15	17	9	106

Data are from the National Registry of Childhood Tumours.[4]
*Other sites: arm/shoulder (five), thorax (nine), abdomen/pelvis (five), trunk not otherwise specified (four), omentum (one), ovary (one), bladder (one).

Table: **Distribution of non-CNS rhabdoid tumours in the UK, 1993–2010**

antibody (figure 1).[8] Loss of expression of *SMARCB1* has also been shown in other tumours—epithelioid sarcomas, epithelioid malignant peripheral nerve sheath tumours, extraskeletal myxoid chondrosarcoma, renal medullary carcinoma, myoepithelial carcinoma—that might have been included in the adult rhabdoid tumours in the SEER programme.[7,9] Although this group of tumours seems varied, they all have loss of *SMARCB1* expression, often with rhabdoid cytomorphology, and sometimes other immunohistochemical and histological features. However, careful attention to the other immunohistochemical findings and appropriate use of confirmatory cytogenetic studies will usually aid appropriate tumour classification.[9]

Results have been reported from the only population-based aetiological study of rhabdoid tumours.[10] This record-based case-control study included 105 cases ascertained from the California Cancer Registry. The patients were all younger than 6 years at diagnosis. 61 had extracranial rhabdoid tumour and 44 had atypical teratoid or rhabdoid tumour. More than 200 000 controls were randomly selected from California birth registers and frequency-matched by birth year to all childhood cancer cases. Results were presented as odds ratios (OR) adjusted for birth year, maternal age, maternal ethnicity, and method of payment for antenatal care (as a proxy for income level). The risk of extracranial rhabdoid tumour was significantly raised for children with low birthweight (<2500 g; OR 2·43, 95% CI 1·09–5·41), gestation of less than 37 weeks (2·63, 1·34–5·17), gestation of more than 42 weeks (3·66, 1·54–8·71), or who were a member of a multiple birth (3·08, 1·11–8·55). Similar results were obtained for atypical teratoid or rhabdoid tumour with respect to low birthweight and multiple births.

Biology and genetics

The first genetic feature identified in rhabdoid tumours, irrespective of anatomical location, was monosomy 22. Translocations and deletions of the 22q11.2 cytoband were subsequently identified.[11] Positional cloning identified the biallelic inactivation of *SMARCB1*, located at 22q11.2, as the main oncogenic event in rhabdoid tumour formation.[12]

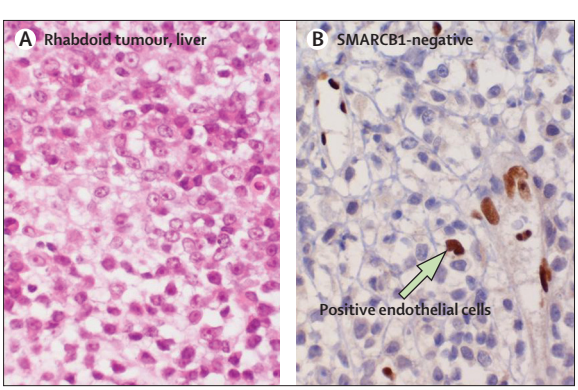

Figure 1: **Rhabdoid tumour of the liver (A), and tumour cells showing loss of staining for SMARCB1 (B)**
Note the internal positive control in the form of the endothelial cells.

The complete inactivation of this tumour suppressor gene results from various combinations of large interstitial chromosome 22q deletions encompassing the whole gene (in about half of cases), whole exon duplication or deletion, oligonucleotide insertions or deletions leading to frameshift and subsequent premature stop codons, and nonsense mutations (in about 25% of cases).[13–15] Homozygous deletions might be more frequent in extracranial tumours. Missense mutations seem to be exceptional. In some rare cases, classic analysis of the coding sequence (ie, direct sequencing and quantitative PCR) does not identify the second hit. In some cases, base pair substitutions in the 3′ untranslated region have offered putative explanations; otherwise, intronic base pair variations leading to the illegitimate insertion of a pseudoexon in the transcript might also account for the full inactivation of *SMARCB1* in rare rhabdoid tumours. In all cases the genetic abnormalities lead to a total loss of protein expression, as shown by immunohistochemistry.[16,17]

The mechanisms underlying the chromosome 22q11.2 rearrangements are mostly unknown; however, the first hit might be present at a germline level in 15–30% of cases.[14,18,19] On rare occasions germline mutations are inherited from asymptomatic parents, either because of gonadal mosaicism or incomplete penetrant mutations.[20] In cases harbouring a germline deletion, precise mapping of the breakpoints has suggested that the low-copy repeats of the 22q11.2 region are particularly targeted by the chromosomal rearrangements, and so-called fragile sites might account for the location of the chromosomal breakages.[19,21] The presence of germline alterations of *SMARCB1* predisposes these individuals to rhabdoid tumours in the brain and extracranial sites, often with several primary tumours.[13] These children tend to be younger, often presenting in the first year of life, and have a poor prognosis. Whether this poor prognosis is because of their young age and therefore the inability to deliver all therapies, the germline mutation itself in all cells, or the presence of multiple primaries, is unclear.[19] Germline *SMARCB1* mutations have also been reported in familial schwannomatosis, but the development of schwannomas is probably by a mechanism distinct from that of rhabdoid tumours in which the SMARCB1 protein is completely absent in tumour cells.[22]

Finally, roughly 5% of rhabdoid tumours do not harbour any mutation in *SMARCB1*. A candidate gene approach in one family has allowed identification of truncating mutations of *SMARCA4* as an alternative genetic event in the rare *SMARCB1*-non-deficient rhabdoid tumours.[23] Similarly to *SMARCB1*, the few *SMARCA4* mutations reported are severe, leading to a complete loss of gene expression.[24] Although small, the exact proportion of rhabdoid tumours that are *SMARCA4*-dependent needs further investigation.

Another striking feature of rhabdoid tumours is their remarkably stable genome. McKenna and colleagues[25]

showed that *SMARCB1* deficiency does not affect the ability of rhabdoid cell lines to maintain genome integrity when exposed to DNA-damaging agents. This experimental observation fits with the remarkably stable karyotypes and largely normal (with the exception of chromosome 22) comparative genomic hybridisation or single nucleotide polymorphism array findings in human rhabdoid tumours.[15,26] High-throughput sequencing assays have confirmed this highly stable genome at the nucleotide sequence level.[27] Kieran and colleagues[27] analysed a restricted panel of more than 900 genes (115 oncogenes) and showed the absence of mutations in the usual oncogenes and tumour suppressor genes (one single *NRAS* mutation in one of 25 tumours). More broadly, Lee and colleagues[28] did whole exome sequencing of 35 human rhabdoid tumours. Strikingly, their results established that rhabdoid tumours harbour the lowest rate of base variations reported in all sequenced cancer types. Apart from *SMARCB1* biallelic inactivation, rhabdoid tumours harbour very few, if any, genetic abnormalities, either recurrent or isolated, which suggests that *SMARCB1* gene mutation is sufficient to promote oncogenic transformation, and acts as a suppressor gene.[29] This information also suggests that potential synergistic events either result from variations in non-coding regions, or from epigenetic deregulation.

Biological features linked to *SMARCB1* deficiency

SMARCB1 encodes the 47 kDa SMARCB1 (also known as BAF47), which constitutes a ubiquitous and indispensable component of the ATP-dependent chromatin remodelling complex SWI/SNF. *SMARCA4*, the second gene inactivated in rhabdoid tumours, encodes another essential member of the SWI/SNF complex—the highly conserved BRG1 protein, which harbours the ATPase activity of the complex. Rhabdoid tumour physiopathology therefore intimately depends on the roles of the SWI/SNF complex.

The main function of the SWI/SNF complex is to control chromatin compaction, and hence gene expression. In particular, the rapid embryonic lethality of *SMARCB1* homozygous deletion in mice suggests a crucial role in early developmental processes.[30] Likewise, significant expression of stem cell-associated factors has been recorded in both profiling of transcriptomes and immunohistochemical studies on rhabdoid tumours.[31,32] To speculate that *SMARCB1* deficiency might severely affect the normal differentiation programme of immature embryonic progenitors, which could be the cells of origin of rhabdoid tumours, is tempting. The prodifferentiation function of *SMARCB1* has consistently been addressed in various rhabdoid cell lines, and seems to affect different mesenchymal or neural lineages.[33,34] Several experimental studies show antagonistic roles between the SWI/SNF complex and the polycomb repressor complex (PRC2; figure 2).[35,36] In particular, Wilson and colleagues[36] showed that the regulation of the stem cell-associated programme, which is maintained by the repressive effect of the *EZH2*-dependent PRC2, is disrupted by *SMARCB1* re-expression.[36] This process needs to be proven, but these results allow speculation about the basic pathophysiology for rhabdoid tumours: that the inactivation of *SMARCB1* in early progenitors or stem cells might enforce the repressive function of the EZH2/PRC2 complex, maintain progenitors or embryonic stem cells in an undifferentiated state, and therefore affect the expression of dozens of oncogenes and tumour suppressor genes.

Kia and colleagues[35] focused on the consequences of this antagonistic phenomenon at the p16 locus. They showed that the restoration of *SMARCB1* expression in rhabdoid cell lines displaces EZH2 from the p16 promoter and subsequently modifies the methylation status of H3K27 histones. The results of this study emphasise the direct modifications of histone methylation in *SMARCB1*-dependent oncogenesis, and the effect of *SMARCB1* inactivation on cell cycle control. The fact that *SMARCB1* deficiency results in an increased G1-to-S transition, and acts upstream of RB phosphorylation, is accepted.[37,38] Apart from defective expression of p16, higher expression of cyclin D1 might also be necessary for this oncogenic process.[39]

Various in-vitro assays examining the re-expression of *SMARCB1* in rhabdoid cell lines have pointed out several other biologically relevant genes and cellular processes; these include *MYC*, *GLI1* and the sonic hedgehog pathway, aurora kinase A, RhoA-GTPase related cytoskeleton dynamics, and *BIN1*.[40–43] Although

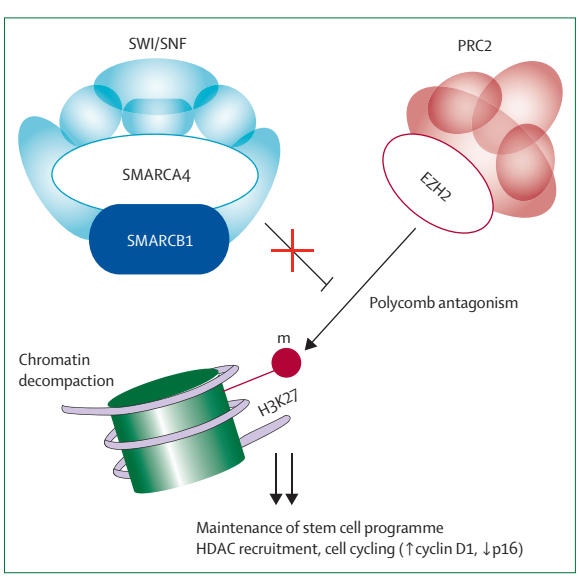

Figure 2: **Antagonistic effects of SMARCB1 within the SWI/SNF complex and PRC2 complex**
The SWI/SNF complex is an antagonist of PRC2. After inactivation of the two *SMARCB1* alleles in rhabdoid cells, the methylation (red circle, *m*) of histone H3K27 is no longer inhibited (red cross), and the repressive pattern of methylation-characterising stem cells is maintained. Such a process affects in particular the p16 locus, leading to a reduced expression of this cell cycle repressor. Together with an increased expression of cyclin D1, the reduced expression forces cells to enter the S phase of the cell cycle. HDAC=histone deacetylases.

weak, transcriptome profiling—mostly done on a small number of extracranial rhabdoid tumours[31]—shows discrepant results about these lists of genes, but does offer some putative candidates for targeted therapies. Expression profiling might also help to decipher the specific diagnostic markers for cranial and extracranial tumours, and could give clues to enable rhabdoid tumours to be distinguished from other *SMARCB1*-deficient tumours.

Clinical features: renal versus extrarenal rhabdoid tumours

The initial clinical reports of extracranial rhabdoid tumours were separated between renal and extrarenal sites, either in single or multiple case reports, often in pathological journals with a focus on distinguishing between the renal and extrarenal site.[3,44–46] Wick and colleagues' review[47] summarised over 70 of the early case reports and suggested the concept that malignant rhabdoid tumours are a distinct pathological entity that occurs at renal and extrarenal sites, and in the brain where they are termed atypical teratoid or rhabdoid tumours. The later genetic characterisation of these tumours showed that most had a mutation of *SMARCB1*, and despite the variability of their clinical behaviour are the same type of tumour.[13]

At the renal site (figure 3), rhabdoid tumours tend to present earlier, usually in the first year of life.[48] In Tomlinson and colleagues' series[49] of 142 renal rhabdoid tumours from the NWTS, the median age at presentation was 10·6 months, with two cases presenting in the newborn period and a male preponderance (male to female ratio of 1·37:1). A further peculiarity of renal rhabdoid tumours is the association with hypercalcaemia, possibly driven by parathyroid hormone secretion.[3,48] Patients who present with renal rhabdoid tumours in the first year of life tend to develop brain tumours that were initially judged to be separate pathological entities but are now recognised as atypical teratoid or rhabdoid tumours or primary rhabdoid tumours in the brain.[49] These individuals are likely to have a germline mutation of *SMARCB1* and have a worse prognosis, probably linked to the early onset of their tumours.[13]

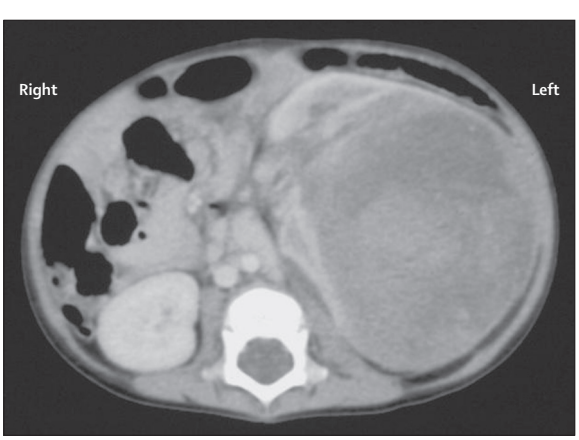

Figure 3: **CT scan of the abdomen at diagnosis showing a left renal rhabdoid tumour**

Non-renal extracranial rhabdoid tumours occur in a range of locations including the liver, soft tissues, peripheral nerves, thymus, salivary glands, gastrointestinal tract, and genitourinary tract.[47] Children with extrarenal non-cranial rhabdoid tumours tend to be older and have a lower stage compared with those with renal non-cranial rhabdoid tumours, with most occurring in the musculoskeletal system.[50] The age range at presentation is broader in extrarenal non-cranial rhabdoid tumours, with some occurring in adults.[50]

Survival

Rhabdoid tumours are often described as lethal, and little evidence of improving survival has been noted. In the 106 children diagnosed with extracranial rhabdoid tumour in the UK from 1993 to 2010, 1-year survival was only 31%.

The 1996 International Society of Paediatric Oncology intermediate nephroblastoma series[48] found 22 cases of rhabdoid tumour of the kidney in 2392 renal tumours in children. Metastases were noted in 82% of cases, either at diagnosis, or developing from 2 weeks to 9 months after diagnosis. Only two patients in the series survived, and both had localised disease (stage II).[48]

In the NWTS series[49] of 142 renal rhabdoid tumours between 1969 and 2002, overall survival at 4 years was 23·2%. An important factor for outcome was stage at diagnosis—4-year overall survival was 41·8% for stage I–II tumours compared with 15·9% in those with stage III, IV, or V disease. Sultan and colleagues' publication[50] from the SEER programme also confirms stage to be an important prognostic factor for outcome. In a multivariate model applied only to children and adolescents with extracranial rhabdoid tumours, tumour stage is a significant predictor of survival (p=0·00014).

A second prognostic factor is age at presentation. In Tomlinson and colleagues' series[49] from NWTS of renal rhabdoid tumours, survival increased with age—4-year overall survival was 8·8% for infants aged 0–5 months and 41·1% in children older than 2 years. This factor is confirmed by the SEER programme, which includes all sites—cranial, renal, and extrarenal—with the worst outcome for those younger than 24 months (hazard ratio 1·79) or older than 18 years (1·83).[50] In the UK, infants (aged 0–12 months) with extracranial rhabdoid tumours had a lower 1-year survival (17·0%) than did older children (aged >1 year) (54·0%).

The NWTS series, and the population-based series from the UK, and the SEER programme all showed no improvement in outcome with time. 1-year survival in children in the UK was 32% in 1993–2000, 31% in 2001–05, and 30% in 2006–10. In the SEER data survival of patients diagnosed in the last 5 years of the study period (2001–05) was not greater than those diagnosed in 1986–2000 (p=0·78).[50]

Small series focused either on extrarenal non-cranial rhabdoid tumours or on liver sites show even worse survival.[51,52] In a series by Bourdeaut and colleagues[51] of extrarenal non-cranial rhabdoid tumours the median time to progression was 5 months (range 0–44), with only one patient remaining free of disease at 7 years. Trobaugh-Lotrario and colleagues[52] reviewed 34 cases of liver rhabdoid tumours identified by a PubMed search of publications from 1970 to 2010. The mean age at presentation was 8 months. 30 patients died, either of disease or treatment complications; most (21) had metastases.[52] In the UK, 1-year survival of children by primary site was 14% for liver, 25% for kidney, 33% for head and neck, and 50% for other sites.

Role of chemotherapy

Since extracranial rhabdoid tumours are rare, no standard therapeutic pathway exists and no randomised trials that examine the role of chemotherapy combinations or addition of new drugs have been done. Instead, we rely on single-arm series, which are often historical, from single institutions. Two case reports of patients with metastatic renal rhabdoid tumours are often cited because of their successful outcome.[53,54] The chemotherapy described in the reports forms the basis for the current Children's Oncology Group study of high-risk kidney tumours, which includes extracranial rhabdoid tumours, and the European Paediatric Soft Tissue Sarcoma Group protocol for extracranial malignant rhabdoid tumours. In both protocols the philosophy of treatment indicates early surgical resection of the primary tumour if feasible, intensive multi-agent chemotherapy, derived from the case reports of Waldron and colleagues[53] and Wagner and colleagues,[54] and local radiotherapy to all sites of disease. Neither study has yet published its results.

In the case reported by Waldron and colleagues,[53] courses of vincristine, doxorubicin, and cyclophosphamide chemotherapy were alternated with courses of ifosfamide and etoposide in an intensive 2-weekly schedule in a child with a metastatic renal rhabdoid tumour. The patient was free of disease 5 years after diagnosis.[53] Similarly, Wagner and colleagues[54] described successful outcomes for two cases of metastatic renal rhabdoid tumours in which ifosfamide, cyclophosphamide, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide were used. The inclusion of doxorubicin in chemotherapy combinations is suggested to be important for survival in extracranial rhabdoid tumours.[53] In Tomlinson and colleagues' series from NWTS,[49] 58% of the patients with renal rhabdoid tumours received doxorubicin, but survival did not differ between those who did and did not receive it.[49] The absence of information about the type and use of chemotherapy from the SEER programme in the Sultan and colleagues series prevented further exploration of this factor in relation to outcome and prognosis.[50]

Further possible evidence for the role of chemotherapy—in particular ifosfamide—is provided by a single historical institutional series from St Jude Children's Research Hospital (Memphis, TN, USA).[55] This series included only 13 children with extracranial rhabdoid tumours, but patients who responded to chemotherapy had regimens containing ifosfamide and hence the authors argue that it has a role in treatment of rhabdoid tumours. It is noteworthy, however, that all patients died.

Although not deemed to be standard of care in extracranial rhabdoid tumours, high-dose chemotherapy with stem-cell rescue is very well reported in intracranial rhabdoid tumours either after relapse or as part of up-front therapy to delay use of irradiation for young children. The role of this treatment in extracranial rhabdoid tumours is not yet clear, although its use in two children with renal rhabdoid tumours has been reported.[56]

The series discussed so far show that recommendation of a standard treatment, or generation of a hypothesis to test additional chemotherapy regimens or drugs is difficult, especially because no phase 2 chemotherapy studies in rhabdoid tumours have been published.

Role of radiotherapy

A small series of renal rhabdoid tumours from NWTS[57] suggests a role of radiotherapy in local control of extracranial rhabdoid tumours. In a later series from NWTS,[49] in which greater numbers of renal rhabdoid tumours were analysed, 100 of the 142 patients in the series received radiotherapy. The overall survival at 4 years was 28·5% in irradiated patients and 12·0% in non-irradiated patients (p=0·25). This effect of radiation was difficult to analyse because radiation tended to be given to those who were older and with higher stage disease; furthermore, the older patients were more likely to receive a higher radiation dose. The positive effect of radiotherapy, particularly of radiotherapy greater than 25 Gy, was thus confounded by age. This effect was lost when the infants aged younger than 1 year were analysed. Only one infant received a dose greater than 25 Gy; therefore, after adjusting for age and stage, which are known prognostic factors, the relative risk of death after 25 Gy was 0·85 (p=0·83) compared with no radiotherapy, and hence the apparent effect of radiotherapy on survival was greatly reduced and no longer significant.[49]

In a multivariate model applied to the SEER programme series, three factors were significant, including use of radiotherapy.[50] In particular, if the multivariate model was only applied to patients younger than 18 years with extracranial rhabdoid tumours, use of radiotherapy remained a significant predictor of survival (p=0·0006). Radiotherapy was only used in 35% of patients, but no significant difference in its use at the different primary tumour sites was observed (p=0·90).[50] However, only 23% of children younger than 3 years received radiotherapy, which was a significantly lower proportion than that of the older patients—46% of patients aged 3 years and older (p=0·0085). The SEER programme does not include data for the dose and volume of the radiotherapy.[50]

For the **Children's Oncology Group** see http://www.childrensoncologygroup.org

For the **European Paediatric Soft Tissue Sarcoma Group protocol** see http://www.epssg.cineca.org/clinical-trials.htm

Search strategy and selection criteria

We searched PubMed using the terms "rhabdoid tumour" and "atypical teratoid/rhabdoid tumour" for references from Jan 1, 1980 to Dec 31, 2012. We included some well respected older references from the authors' own files. We included relevant references from the articles identified by the search strategy.

New targeted therapies

The poor prognosis of patients with rhabdoid tumours who have chemotherapy suggests the use of targeted therapies for future treatment strategies. Since *SMARCB1* has a crucial role in the G1-to-S transition, a first strategy consists of targeting of cell cycle control. The combination of fenretinide and 4OH-tamoxifen induces apoptosis and cell cycle arrest in rhabdoid cell lines, and cell cycle arrest, connected to the strong repression of cyclin D1.[58] To restore cell cycle control the pan-CDK inhibitor alvocidib has been used in xenografted mice and genetically engineered models.[59,60] The efficient stabilisation and reduction of these tumours is promising and suggests a role for CDK inhibitors in clinical trials. Smith and colleagues[59] also noted a silencing of cyclin D1 expression after alvocidib treatment, which suggests that this compound might affect the cell cycle through various pathways.

A second strategy comes from preclinical data obtained with histone deacetylase (HDAC) inhibitors. The main rationale for these inhibitors is the effect on the methylation or acetylation patterns of histones in rhabdoid tumours, supported by the antagonistic effects of PRC2 and SWI/SNF complexes on histone modifications. Moreover, part of the SWI/SNF complex activity relies on regulation of HDAC recruitment to the loci of their target genes; therefore HDAC inhibition might restore some of the regulation processes that are lost in a *SMARCB1*-deficient context.[61] In that light, results of in-vitro studies have shown an interesting effect of romidepsin on cell growth and apoptosis,[62] possibly related to induction of autophagy in rhabdoid tumour cell lines.[63] Sodium valproate, a common anticonvulsant used in children, has shown some HDAC inhibition properties, and is therefore a possible candidate for therapy. However, the doses needed for inhibition might not be easily achieved in clinical practice. The suberoylanalide hydroxamic acid (SAHA) HDAC inhibitor vorinostat has also shown promise in phase 1 trials in adults[64] and children with refractory solid tumours;[65] however, efficacy in rhabdoid tumours has not yet been proven.

Despite the wide interest in tyrosine kinase inhibitors in early clinical trials, few studies have assessed their potential benefit in rhabdoid tumours,[66,67] probably because of the reduced expression in rhabdoid tumours. However, the identification of the serine–threonine aurora kinase A as a downstream target of *SMARCB1* might suggest a role for aurora kinase inhibitors in rhabdoid tumours.[41] As for SAHA, aurora kinase A might have a radiosensitiser role.[68] A phase 1 trial of AT9283—an inhibitor of aurora kinase (NCT00985868)—could show a more realistic targeted therapy in rhabdoid tumours than those drugs suggested by murine models or cell lines, which might not reach paediatric clinical practice.

Where next?

Extracranial rhabdoid tumours continue to be aggressive tumours with poor survival rates. Young age at presentation often limits delivery of multimodal therapy—particularly radiotherapy—which seems to have an important therapeutic role. Further research is needed to gain understanding of rhabdoid tumour biology and the true cell of origin, and further knowledge of the role of *SMARCB1* in rhabdoid tumour development. This knowledge could identify more and better targets for therapy, and could also benefit other tumours from the SMARCB1-deficient family of tumours that might have the same targets.

Although no standard therapeutic pathway exists for rhabdoid tumours, the outcome from the current EpSSG and COG studies might at least establish a standard chemotherapy backbone to add small molecule inhibitors to what are known targets. Some of these are in paediatric phase 1 trials in the UK, such as AT9283. We might need to take a leap of faith on the basis of cell line data and preclinical mouse models to put these agents straight into phase 3 clinical trials while not having data from phase 2 trials in rhabdoid tumours; at least toxicity data will be available from phase 1 and 2 studies in more common paediatric tumours. The outcome of patients with rhabdoid tumours is unlikely to improve with current chemotherapy, which is already at maximum tolerance; new targeted agents, to be given in combination, are needed.

Contributors

CS wrote the incidence and epidemiology section, and prepared the table. FB wrote the biological and new targeted therapies sections, and prepared the figure. BB wrote the rest. All authors revised and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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