Guidelines for management of Atypical Teratoid Rhabdoid Tumours

CCLG Neuro-oncology Special Interest Group

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This document refers only to patients with a diagnosis of primary CNS rhabdoid tumour, which is Atypical Teratoid Rhabdoid Tumour. There is guidance provided for non-CNS tumours (Rhabdoid tumour of the kidney and Extra-renal Rhabdoid Tumour) within the EpSSG Non-Rhabdomyosarcoma (NR-STS 2005), and clinicians are encouraged to register these patients within the EpSSG study.

Synopsis

ATRT is an uncommon, but increasingly recognized tumour of infants and young children. The prognosis until recently has been dismal, but several treatment strategies have appeared in recent years which report improved outcomes. The basis for these strategies include: accurate diagnosis, radical resective surgery, intensive multi-agent chemotherapy, including intrathecal chemotherapy and the use of local radiotherapy. High dose chemotherapy is an alternative in patients where radiation is not considered appropriate.

Molecular genetic analysis is considered essential for all tumours, and this can now be offered at two laboratories in the UK, and two in Europe. There is a high incidence of germ-line mutation, and genetic counseling is recommended for all patients.

Background

Rhabdoid tumours

Rhabdoid tumours of the kidney (RTK) were first described by Beckwith and Palmer as a sarcomatous variant of Wilms' tumour, characterized by more aggressive behaviour and poorer survival(1). Shortly thereafter, rhabdoid tumours were observed in almost any anatomical site, including the central nervous system (CNS). It was not unusual for this tumour to present congenitally, often with disseminated or multicentric tumours.

Rhabdoid tumours are rare entities, comprising fewer than 1% of childhood malignancies. The true incidence of this tumour is not yet known, but the diagnosis is increasingly made as pathologists become familiar with it, and as immunohistochemical techniques allow its separation from other, embryonal tumours of infancy and childhood.

Rhabdoid tumours in the CNS may comprise rhabdoid cells or may display a combination of characteristics of rhabdoid cells and a population of neuroepitelial, mesenchymal and epithelial cells, as described by Rorke *et al.*, who coined the term "atypical teratoid/rhabdoid tumour" (ATRT) (2).

Cytogenetics

Combined cytogenetic, fluorescence in situ hybridization, and molecular genetic studies demonstrated the presence of cytogenetic abnormalities, such as monosomy or deletion of chromosome 22, in some cases of rhabdoid tumours. A gene within chromosome 22q11, the putative tumour suppressor SMARCB1/hSNF5/INI1, has been identified as a candidate tumour suppressor gene for rhabdoid tumours of all anatomical sites. These data suggest that ATRT and other rhabdoid tumours should be regarded as the same entity.

Familial occurrence of this tumour has been reported. The presence of constitutional mutations of SMARCB1 documented in these cases led to the identification of a predisposition syndrome according to the "two-hit hypothesis". The identification of a Rhabdoid predisposition syndrome is increasingly identified, and seems to be most likely found in those patients diagnosed in the first year of life(3-5).

Recent advances in pathological diagnosis have lead to the availability of immunohistochemical stains specific for the SMARCB1 protein; this has increased the accuracy of histological diagnosis of the disease, but the appropriate interpretation of SMARCB1 stains, in the context of a prospective study, remains to be defined. There are now reported cases of ATRT in which expression of SMARCB1/INI-1 is preserved, although these are infrequent(6). Clinical and basic genetic studies are still needed in order to better correlate genotype and phenotype.

ATRT

Rhabdoid tumours of the CNS, ATRTs, present clinico-pathologic features which are distinct from medulloblastomas and sPNET, with an unusually poor prognosis and with the highest incidence in the first two years of life. In the past, many may have been misdiagnosed as medulloblastoma due to clinical and light-microscopic similarities, but the availability of antibodies to the gene

product of INI-1 allows reliable separation of these. The true incidence of rhabdoid tumours is still largely unknown.

The characteristic pathological change of both non-CNS rhabdoid tumours and ATRT is mutation of the INI1 (SMARC-B1, hSNF5) gene. The presence of a common mutation may indicate that a unified treatment approach could be adopted, although the associated problems of primary CNS tumours, particularly in very young patients may make this impossible.

The management of intracranial rhabdoid tumours (ATRT)

Management of ATRT has, until recent years, been variable, with limited success. Early case reports of successful treatment with a strategy based on IRS treatment lead to this approach being taken on an individual basis, but formal studies have only recently been reported

Olson et al (7)reported three patients with newly diagnosed CNS ATRT who achieved prolonged remission following surgery, radiation and chemotherapy (systemic and intrathecal) based upon a protocol for children with rhabdomyosarcoma with parameningeal extension (IRS III Regimen 36). Two of those three patients are long-term survivors.

Weinblatt and Kochen (8)published a single case report of sustained remission of CNS ATRT after surgery, radiation and the same IRS III based therapy.

Registry data

Registries of ATRT(9, 10) have provided useful information supporting the role of surgery, chemotherapy and radiotherapy.

ATRT registry Cleveland (Hilden et al., 2004)

This registry included 42 patients of whom 20 received RT. Nine of the children received local radiotherapy, and four received craniospinal irradiation. Median survival was 48 months (range 10 to 96 months). Eight children were alive at the time of publication. Local RT appeared to have positive influence on survival.

Survivors had received a combination of neurosurgery, radiotherapy and chemotherapy regimens, mainly using Cisplatin, Etoposide, Vincristine, Ifosfamide, Doxorubicin, Actinomycin D, Cyclophosphamide. Intraventricular or intrathecal chemotherapy was used for some.

ATRT registry Memphis (Tekautz et al., 2005)

This registry was reported with retrospective data on 31 patients with the following characteristics:

22/31 were younger than 3 years old.

Following surgery, 30/31 patients received chemotherapy.

21/31 received RT. Ten received RT as part of primary therapy, and 8 of these were alive at the time of analysis.

Most patients diagnosed after the age of three were treated with chemotherapy and radiotherapy. Three of four patients who suffered from progression during therapy could be salvaged by treatment with ICE.

In this report, age at diagnosis was the only statistically significant prognostic factor: most of the patients who died were under 3 years.

German (HIT) data

In the databases of the German HIT studies (1988-2004) 57 patients with the reference pathology diagnosis of ATRT have been identified. 22 were female, 35 male. 29 patients were younger than 1.5 years, 18 were older. Tumours were evenly distributed between the supra- and infratentorial location (n= 27). 28 patients had no metastases at the time of diagnosis (M0). Patients with metastases were younger than those without.

Complete neurosurgical resection was possible in 18/57 cases and subtotal or partial removal was possible in a further 18. Two cases underwent biopsy alone. 27 patients received radiotherapy, 55 patients received chemotherapy.

With a median follow-up of 3.5 years, three-year EFS was 22%, and OS was 16 % respectively. Twelve patients had shown no tumour progression after more than one year from the end of treatment (range 1.1 to 10.7 years). Seven of these patients are in complete remission.

Tumor progression was seen in 60 % following initial post-operative chemotherapy. Positive and statistically relevant prognostic factors were

- age above three years,
- absence of metastases and
- complete response to chemotherapy.

Intrathecal therapy had no significant impact on survival, but was not formally tested as an endpoint (Rutkowski personal communication).

HIT ATRT registry

Between 1988 and 2004, 65 children with ATRT were diagnosed. 28 of 65 children (mostly infants) underwent surgical resection and then chemotherapy alone. 36 patients received radio- and chemotherapy. 44 (68.8 %) were below three years of age, 18 of these were treated with a combination of radiotherapy and chemotherapy.

Median PFS and OS after primary radiotherapy were 22 months and 31 months, compared to 4 months and 9 months for those receiving chemotherapy alone. The 2-yrs PFS and OS following local radiotherapy were 59% and 54%, and after craniospinal RT,46% and 46% (p = n.s.).

No difference was seen between PFS or OS for patients receiving radiotherapy as part of initial therapy, or at the time of relapse. Two year PFS and OS following primary RT were 53% and 55%, and following salvage RT, 52% and 58%.

UKCCSG/CCLG Data

A review of UK patients with ATRT was performed in 2006, and 51 patients were identified (SPL, unpublished). These patients were treated with many different regimes, most being based upon MMT or EuroEWING(sarcoma) regimes, or PNET-MB (PNETIII, St Jude's protocol). Ten patients were alive

at this time, with a mean survival for these of 5.9 ± 3.4 years, consistent with other reported data.

Chemotherapy with MMT95 or 98, or PNET III was most likely to have been associated with survival. Complete surgical resection of the tumour at diagnosis was strongly associated with survival. Few patients who did not receive radiotherapy survived, although three had received high dose chemotherapy and were alive at the time of review.

The role of surgery in ATRT

There is a clear benefit for patients who achieve surgical CR in most reported cases. In the report by Hilden(9), 10/21 patients remained alive having achieved a surgical complete clearance, compared to 4/21 who did not. Comparable data were found for the patients identified in the UK review (6/13 alive after surgical CR compared to 4/20 where this was not achieved and 0/14 where information was not available.

Further support for surgical resection being of prognostic value comes from the recent DFCI study (see below).

The role of radiotherapy in ATRT

Radiotherapy has been used for the majority of patients treated successfully for ATRT, and it is an important component of current strategies. There is some confounding of data, however, since patients who have not received radiotherapy are likely to be those who show early progression, poor clinical state or are very young. Radiotherapy is often part of a systematic approach to treatment, and there may be a beneficial effect from this alone.

The data reported by Hilden(9) showed some benefit associated with RT (8/13 patients alive after radiotherapy compared to 6/29 alive who had not received radiotherapy), although clearly, in this retrospective series, the approach to treatment was by no means standardized. Of those patients who died despite radiotherapy (n=5), four patients progressed early, and one after 60 months.

The report by Tekautz(10) included 22 patients treated according to the SJMB96 protocol. Twenty two patients under the age of 3 years were treated without radiotherapy, of whom only one patient survived. Two patients received radiation therapy in addition to chemotherapy, and both were alive at the time of publication(10).

Conversely, a report by Chen et al, of 17, mainly older patients (only one under 3 years of age) who underwent complete surgical resection and craniospinal radiation therapy gave an overall survival of only 3/17. In this setting, radiotherapy appeared to be ineffective(11).

In the UK, 51 patients were reviewed, diagnosed from 1993 to 2004. These data remain incomplete, but for those patients who received RT as part of their primary therapy, 8/19 were alive, compared to only 3/16 who did not. Information was lacking for a further 13 patients, all of whom died (SP Lowis, unpublished review).

It seems reasonable to conclude that radiation therapy is associated with a higher rate of local control, and may improve long term survival. Craniospinal RT does not seem to be associated with a higher overall survival.

The role of intrathecal therapy in rhabdoid tumours of the CNS (ATRT)

Intrathecal therapy, even in the presence of bulky disease may not affect outcome. Reports by Chou & Anderson(12) and Weinblatt & Kochen(8) showed no benefit in patients with significant disease after surgical resection.

In the report of Olson et al., three patients were treated with triple intrathecal therapy(7). One patient with persistent disease after radiotherapy survived. The chemotherapy used was based upon the IRS III study for parameningeal rhabdomyosarcoma. In two cases, only a subtotal resection was possible, in one of the three patients metastatic disease to the CSF was seen. All three patients received anthracycline-based poly-chemotherapy and radiotherapy. At the time of publication, all three were alive five years, two years and nine months after diagnosis.

Hilden et al. reported four patients who received intrathecal thiotepa following subtotal tumor resection, chemotherapy and high-dose chemotherapy. At the time of publication one of these patients was alive, 46 months after diagnosis(13).

In the report by Hilden et al. of 42 patients with ATRT, 16 patients received intrathecal chemotherapy and 13 of these received triple therapy (MTX, Ara-C, Hydrocortisone). Seven are free of relapse with a median survival of 23 months. Looking at the 14 patients who were free of disease at the time of publication, 10 of these had a complete resection, six of ten had received intrathecal therapy. Five of these patients also received radiotherapy. The median age of the surviving patients was 30 months at diagnosis; median event-free survival was 42 months.

In 2004 Ronghe et al. reported two patients(14). One patient received triple intrathecal therapy following subtotal resection and chemotherapy as well as high-dose chemotherapy followed by autologous bone-marrow rescue. This patient was alive 43 months after diagnosis and without any neurological side effects. The second patient received a subtotal resection followed by poly-chemotherapy and intrathecal therapy as well as RT. This patient was also alive 55 months after diagnosis without any signs of disease. Both patients are alive as of July 2010.

In 2005 Zimmerman et al. reported four patients with ATRT (n=2 new diagnoses, n=2 relapses) (15). All four received poly-chemotherapy including 11 doses of triple intrathecal therapy (MTX, ara-C, hydrocortisone). Patients with a new diagnosis were irradiated. One of the patients received stereotactic RT. All four patients were alive without evidence of disease at the time of publication.

The role of high dose chemotherapy (HDCT) therapy in rhabdoid tumours

High dose therapy is used as an alternative to radiation therapy for patients where significant morbidity is likely, and as an adjunct to radiotherapy where

further dose intensification of chemotherapy is sought. Whilst there has been no formal study of high dose chemotherapy, data are available from case reports. The value of high dose therapy is difficult to determine in these patients, given that they are likely to be a selected group, younger, or with incomplete response to surgery and/or radiotherapy.

- Hilden et al. in 1998 reported two patients who received stem cell transplants in the course of their treatment for ATRT(13). One patient underwent subtotal resection, received two courses of conventional chemotherapy and then weekly vincristine and intrathecal thiotepa for six weeks. 13 months following diagnosis autologous stem cell transplantation after conditioning with melphalan and cyclophosphamide was performed. At the time of publication the patient was without evidence of disease for 46 months with only minor neurological deficits and deafness.

  The second patient (aged 18 months) underwent subtotal resection and then two courses of cisplatin and etoposide followed by weekly vincristine and intrathecal thiotepa. Two additional cycles of chemotherapy using ifosfamide and doxorubicin ensued, but the patient developed metastatic recurrence at six months from diagnosis. Reinduction chemotherapy with etoposide, cyclophosphamide and seven doses of intrathecal therapy (ara-C, MTX, prednisone) was followed by high-dose chemotherapy (melphalan, busulfan and thiotepa) with ASCR. Disease progressed and radiotherapy was administered, but the tumour continued to progress and the patient died.

- Katzenstein et al. reported a 21 months old patient with a malignant rhabdoid tumor of the liver, local lymph node metastases and distant lung metastases. Initial treatment consisted of cisplatin, amifostine, vincristine, 5-FU, ifosfamide, carboplatin, etoposide, cyclophosphamide and doxorubicin(16). Subsequent to this induction, high-dose chemotherapy with a tandem approach of etoposide, carboplatin and cyclophosphamide for the first cycle and melphalan and cyclophosphamide for the second cycle was applied. Despite these aggressive measures the tumour progressed and the patient died nine months following diagnosis.

- In 2003 Sahdev et al. published a report on identical twins both with rhabdoid tumours of the kidney(17). The first patient was diagnosed at the age of five months. Following complete resection of the tumor metastases to the lung and brain were demonstrated. Despite chemotherapy using carboplatin, etoposide and cyclophosphamide, the disease progressed. The patient received two cycles of taxol, but died at the age of 12 months. The second child became symptomatic at the age of two years. He also suffered from metastases to the lung and brain. Following subtotal resection and six cycles of chemotherapy using cisplatinum, doxorubicin, vincristine, cyclophosphamide, actinomycin D, etoposide and ifosfamide the tumor presented with a good response. Due to proven chemosensitivity of the tumour high-dose therapy using etoposide, thiotepa and cyclophosphamide was

performed. At the time of publication the patient was alive without evidence of disease at six years.

- Ronghe et al. reported on the successful treatment of one patient. This 14 months old girl with ATRT was subjected to a subtotal resection(14). She then received induction chemotherapy using vincristine, dactinomycin, ifosfamide, epirubicin, carboplatin and etoposide. In addition she received nine doses of intrathecal triple chemotherapy. To avoid RT, consolidation was performed by high-dose chemotherapy using busulfan and thiotepa. At the time of publication the patient was without evidence of disease 52 months following diagnosis.
- Hilden et al. reported on a larger series of patients with ATRT(13). In their series of 42 patients 13 received consolidation using myeloablative therapy with stem cell rescue in addition to induction chemotherapy. In eight patients single high-dose chemotherapy was performed. Five of these were alive without evidence of disease at the time of publication, three died between 10 and 22 months following diagnosis. In an additional five patients high-dose chemotherapy was performed in the form of three mini-transplants. Of these, only one patient was alive 48 months following diagnosis.
- Dallorso et al. reviewed the role of high-dose chemotherapy in brain tumors overall(18). In a series of 29 ATRT patients included into the AIEOP trial 13 patients received myeloablative chemotherapy. The event-free survival at five years did not differ between patients who received conventional chemotherapy and those who received high-dose chemotherapy. Thus, the authors concluded that the role of high-dose chemotherapy has to be judged as questionable.
- In 2005 Fujita et al. published the case of a newborn with a tumor of the orbit(19). At the age of 10 months the eye was enucleated and histologically proven to be affected by ATRT. On imaging a further lesion was found in the fourth ventricle of the CNS. This lesion was completely resected. The patient received induction chemotherapy using cisplatinum, etoposide, ifosfamide, carboplatin, vincristine and nimustine. Consolidation consisted of thiotepa, melphalan, followed by autologous stem cell rescue. At the time of publication the patient was alive without evidence of disease 24 months following surgery.
- In 2006 Watanabe et al. report on a 15 months old boy with MRT of the orbit(20). Following subtotal resection induction chemotherapy was applied, consisting of cisplatinum, etoposide and vincristine. As there was no response, therapy was augmented with doxorubicin and ifosfamide. After two cycles clinical and radiological response was demonstrated. The parents refused radical surgery, and gamma-knife surgery was used with high-dose chemotherapy. A first cycle of high-dose chemotherapy consisted of melphalan and cyclophosphamide, the second of ifosfamide and thiotepa. At the time of publication the patient was alive four years following diagnosis.
- In 2006 Beschorner et al reported on a 14 months old boy with ATRT(21). Following subtotal resection and induction chemotherapy one year from diagnosis relapse occurred. Reinduction chemotherapy

consisted of carboplatin, etoposide and thiotepa. Following surgery high-dose chemotherapy using carboplatin, thiotepa, etoposide and MTX was performed. The patient received local RT 54Gy, and stayed in remission for eight years following diagnosis but did relapse. After relapse surgery the patient was submitted to cyber-knife RT. At the time of publication the patient was alive at three months.

- Madigan et al. reported a series of 14 patients with extracranial rhabdoid tumors treated between1983 and 2003, with 5 long-term survivors(22). All of these had radical surgery and chemotherapy with or without RT, and two received high-dose chemotherapy followed by stem cell rescue. One patient was a six months old boy with a rhabdoid tumor of the kidney, who received high-dose carboplatin, etoposide and melphalan without RT. He was alive, NED, 34 months following diagnosis at the time of publication. The second patient was a 30 months old girl with a rhabdoid tumor of the neck. She received high dose therapy with carboplatin, etoposide and melphalan, and RT (45 Gy) locally. This patient was without evidence of disease 104 months from diagnosis at the time of publication.
- In a congress report, Garrè et al. presented the Italian experience of the AIEOP on infants with ATRT treated from 1995-2003. All patients had been enrolled on medulloblastoma-like protocols. Eleven patients were treated on standard chemotherapy protocols, while 13 received HDCT. 5 year PFS did not differ between the two groups (18.2% vs. 15.4%).
- ISPNO 2010: Lafay-Cousin reported a retrospective review of 48 patients (median age at diagnosis18.5 m, range 0–188) (23). Eleven underwent palliation. Among the 37 remaining, 13 received high dose chemotherapy. Fifteen patients received upfront radiation. 30/ 37 treated patient relapsed/progressed, median survival time 12.5 months (5.7–19.2)., 9 patients were alive with a median follow-up of 40.8 months. Patients who received HDC regimen had better outcome (2 y OS 52 ± 14 versus 21 ± 8%, p <0.027). Upfront radiation did not provide a survival benefit for this group of 48 patients

High dose therapy has largely been reported for individual patients, with only two series with larger cohorts of patients. Whilst the relative importance of HD therapy compared to radiotherapy cannot be assessed from this, it is reasonable to conclude that it may be of value in those patients where RT is considered too hazardous.

Published literature on rhabdoid tumor patients treated with HDCT (taken from EuRhab protocol)

Author	n =	Age (months)	surgery	HDCT	Survivors [n =]	Adjuvant therapy survivors	Adjuvant therapy non-survivors
Hilden (1998)	2	Pat 1: 38 Pat 2: 18	Pat 1: PR Pat 2: PR	Pat 1: melphalan, cyclophosphamide Pat 2: melphalan, busulfan, thiotepa	1 (Pat 1)	CT, IT-Chemo thiotepa, RT	CT, ITT + thiotepa, stereotactic radiosurgery, RT
Katzenstei n (2003)	1	21	biopsy	1.: etoposide, carboplatinum, cyclophosphamide 2.: melphalan, cyclophosphamide	0		CT
Sahdev (2003)	1	24	PR	etoposide, thiotepa, cyclophosphamide	1	CT	
Ronghe (2004)	1	14	PR	busulfan, thiotepa	1	CT, ITT	
Hilden (2004)	13	DOD: 7,14,22,31, 46,52,72 NED: 6,19,22,40, 44,49	DOD: TR: 4, PR: 3 NED: TR: 3,PR: 3	varying regimen	6	CT: 6 RT: 2 intrath. CT: 2	CT: 7 RT: 3 intrath. CT:2
Tekautz (2005)	2	?	?	?	?	?	?
Dalloro (2005)	13	?	?	?	?	?	?
Fujita (2005)	1	1	TR	thiotepa, melphalan	1	CT	
Watanabe (2006)	1	15	PR	1.: melphalan, cyclophosphamide 2.: ifosfamide, thiotepa	1	CT, gamma-knife-surgery	
Beschorne r (2006)	1	14	PR	carboplatinum, thiotepa, etoposide, MTX	1	CT, RT, gamma knife surgery	
Madigan (2007)	2	Pat 1: 6 Pat 2: 30	Pat 1: TR Pat 2: PR	Pat 1 und 2: carboplatinum, etoposide, melphalan	2	Pat 1: CT Pat 2: CT, RT	

Recent investigational protocols

Reports of long term survival after treatment with RMS-type chemotherapy lead to this approach being adopted by several groups, and to subsequent institution-based approaches based on these lines.

These cases lead to the approach taken at the Dana-Farber Cancer Institute using the IRS III based therapy. Patients included two newly diagnosed and two recurrent CNS ATRT who were long term survivors.

A multi-institutional phase II study to test the efficacy of aggressive surgical resection, multi-agent systemic and intrathecal chemotherapy with radiation therapy for children with newly diagnosed Central Nervous System Atypical Teratoid/Rhabdoid Tumour was proposed by DFCI, and this study subsequently enrolled 25 patients, of whom 20 were eligible for analysis of survival.

The DFCI study (02-294), published by Chi et al (24)had the following design:

- Following diagnosis, patients underwent maximal surgical resection. Patients were reported as GTR, Subtotal or biopsy according to surgical opinion and MRI after surgery.

- All patients underwent brain and spine MRI, CSF examination, CT chest and abdomen, bone marrow aspiration and trephine. Staging was according to that of Chang (25)
- Chemotherapy was begun within 50 days of surgery. Blocks of chemotherapy were given as follow:

  1/ Pre-irradiation induction (weeks 1-6)

  2/ Chemo-radiation induction (weeks 7-12)

  3/ Post-irradiation induction (weeks 13-18

  4/ Maintenance (weeks 19-44)

  5/ Continuation ± Doxorubicin (weeks 45-51)

Outcome from this study

Two year PFS was 53±13% and OS 70 ±10%.

Of the 20 evaluable patients in this study, 14 had initially localized disease (M0), 1 had M2 and 5 had M3. Eight had to come off study at some stage: one died from treatment-related toxicity, 4 developed progressive disease in the first 13 weeks, 1 developed radiation recall at week 50, 1 transverse myelitis at week 21 and one because of non-compliance. This latter patient was subsequently treated with radiotherapy, but developed progressive disease and later died.

Metastatic stage was prognostic. Eight of fourteen patients with localized disease were alive, NED. One patient achieved PR which was stable after RT, and remained alive with disease. One other had relapsed after CSRT after achieving CR. One patient with M2 disease remained alive with disease. Four of five with M3 disease died of disease, but one achieved CR with induction chemotherapy, received CSRT and remained alive, NED.

The degree of surgical resection was of prognostic value. Three patients underwent biopsy alone, and all died rapidly. Five of seven who had subtotal resection and 9/10 who had gross total resection were alive at the time of publication.

Response to chemotherapy was prognostic. Seven of seven in continued CR, and a further 2 of 2 who achieved CR after induction chemotherapy were alive with NED at publication. One of 6 with a mixed or PR remained alive (with disease). This patient had stable disease after radiotherapy. Three patients had stable disease after induction. One achieved CR after RT and remained alive, NED. One had continued SD after RT, and remained alive with disease. One progressed after RT and died.

Fifteen patients received RT on study, 11 focal and 4 craniospinal. Status after radiotherapy was prognostic. All ten patients in CCR (n=9) or CR (n=1) after RT were alive, although one had ongoing disease. Two patients with persistent stable disease remained alive with disease. All others (n=8) had died.

These data are summarized in the table below.

	Age at diagnosis (years)	Primary Tumor Location	Chang Stage	Extent of Resection	Response to Induction	RT Field	Response Post-RT	Time to Relapse (years)	Duration of Survival (years)	Disease Status
1	0.3	PF	M0	GTR	CCR	Conf	CCR		1.6	ANED
2	0.4	Supra	M0	STR	PR	N/A	PD	0.3	0.3	DOD
3	0.8	PF	M0	GTR	CCR	Conf	CCR		1.5	ANED
4	0.9	PF	M2	GTR	SD	Conf	SD		1.5	AWD
5	1.3	PF	M0	GTR	CCR	Conf	CCR		2.9	ANED
6	1.4	Supra	M0	GTR	CCR	Conf	CCR		1.7	ANED
7	1.6	PF	M0	STR	CR	Conf	CCR		2.6	ANED
8	1.6	PF	M3	STR	PR	Off-study	N/A	0.3	1.5	DOD
9	2.2	Supra	M0	STR	SD	Conf	PD	0.6	0.9	DOD
10	2.2	Supra	M0	Bx	PD	N/A	N/A	0.1	0.2	DOD
11	2.4	Supra	M0	STR	PR	Conf	SD		1.4	AWD
12	2.7	Supra	M0	GTR	TD	N/A	N/A	N/A	0.1	D-TD
13	3.1	Supra	M0	GTR	CCR	Conf	CCR		1.9	ANED
14	3.2	Supra	M0	STR	SD	Conf	CR		3.3	ANED
15	4.6	Supra	M3	Bx	PR	N/A	PD	0.2	0.7	DOD
16	5.2	Supra	M3	GTR	CR	CSI	CCR		2.6	ANED
17	5.3	PF	M0	GTR	CCR	Confo	CCR		2.6	ANED
18	7	PF	M3	STR	PR	CSI	PR	1.8	2	DOD
19	8.4	PF	M0	GTR	CCR	CSI	CCR	2.2	2.8	AWD
20	19.5	Supra	M3	Bx	Mixed	CSI	PR	2	2.1	DOD

EuRhab protocol

The EuRhab protocol is the current recommendation for all German patients with rhabdoid phenotype, both CNS and non-CNS. This strategy has been adopted by some other countries for CNS tumours.

Recommendations for treatment were produced in 2005, named later as “Rhabdoid 2007”. Thirty four patients were treated according to these, until November 2009. A further 16 patients had been treated according to the updated recommendations, EuRhab at the time of the presentation (July 2009 to June 2010). Seven patients received no active therapy, and 10 received other, individualized therapy. No further information was available for one patient.

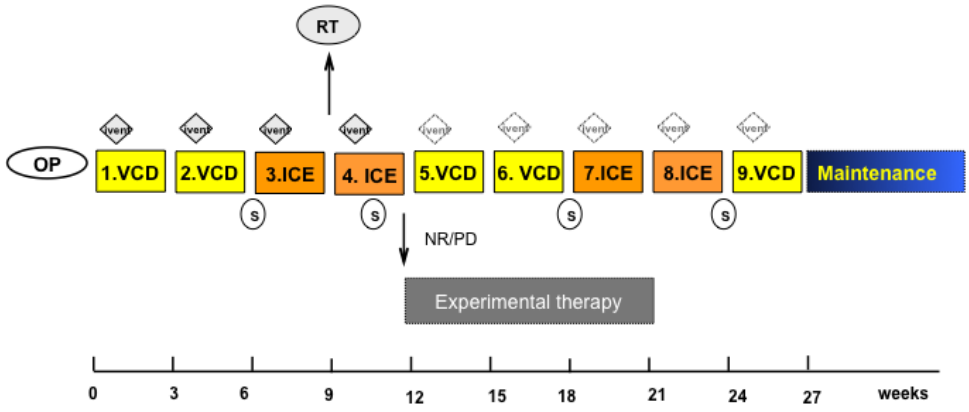
Outcome data from the Rhabdoid tumour recommendations were presented at the SIOP Brain tumour working group meeting in Vienna, 2010. At this time, 132 patients had been registered, 68 with ATRT. Six patients had renal

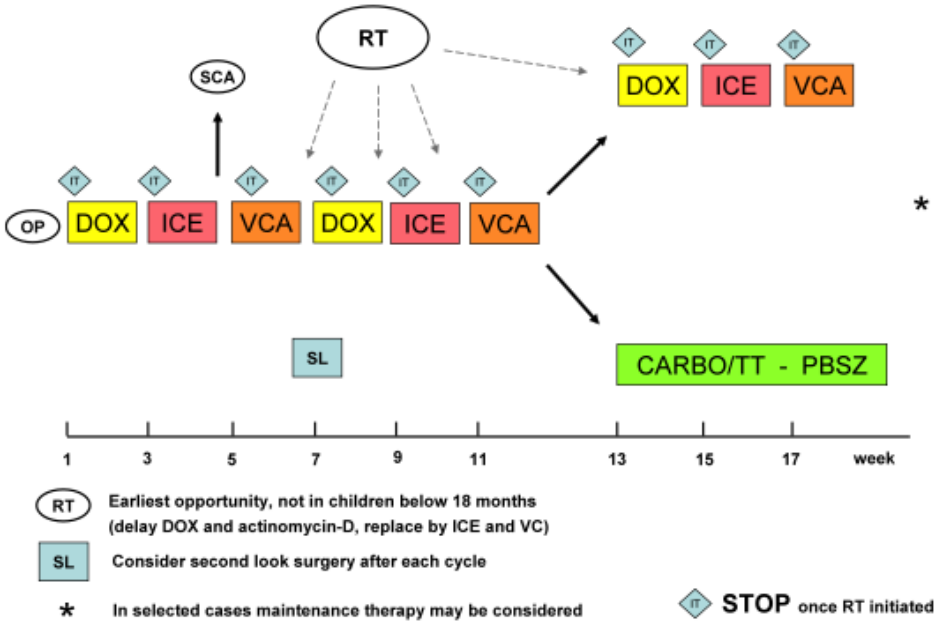
rhabdoid tumours, 17 had extra-renal, non-CNS rhabdoid tumours, 18 were patients registered after consultation only, and 23 were recorded as “other”. The large majority of patients in this registry are therefore primary CNS tumours.

The initial diagnostic specimen had been reported as ATRT in 18 of 47 confirmed specimens. Other diagnoses included glioblastoma, sPNET, PNET-MB, highly malignant brain tumour and no diagnostic information.

Outlines of the Rhabdoid 2007 and EuRhab recommendations are given below.

Rhabdoid 2007 Recommendation





Outcomes for all 47 patients with a confirmed diagnosis of ATRT, treated to either of the two strategies, or other therapies were presented. These were encouraging:

At two years from diagnosis, overall survival was 77 ± 9% with Rhabdoid 2007 (n=24). No patient treated according to EuRhab had yet died, but follow up was short (n=16).

The registry data confirmed an adverse prognosis for patients who

- received no radiotherapy (OS 89±8% (n=26) vs 28±20% (n=21)) and
- were diagnosed before the age of 36 months (OS 54±12% (n=31) vs 93±7% (n=16))

Eleven patients died. Relevant factors in these patients include:

1. Inoperable tumour, no chemotherapy
2. Incomplete resection, individual therapy
3. M0 disease, individual therapy, high dose chemotherapy, proton beam RT
4. M3 disease, incomplete resection, no RT
5. M2 disease, incomplete resection, no RT
6. M0 disease, one cycle of chemotherapy, death from herniation
7. M1 disease, incomplete resection, no chemotherapy received, germ line mutation identified

8. M0 disease, incomplete resection, progression after 5 cycles of chemotherapy (no intrathecals used). Germ line mutation identified
9. M0 disease, incomplete resection, perioperative stroke. Chemotherapy stopped prematurely after 6 cycles because of encephalomalacia. No RT.
10. M? disease, incomplete resection,preogressed after 3 cycles of chemotherapy, no RT
11. M0 disease, incomplete resection, received full course with RT. Died from neurosurgical complication (shnt dysfunction). No evidence of tumour recurrence at 16 months from diagnosis.

Importantly, no patient who achieved CR after surgical resection, and who subsequently completed chemotherapy and radiotherapy, died.

Toxicity of the VCD-ICE or Dox-ICE-VCA regimes was reported to be generally acceptable, but it is likely that toxicity will be substantially under-reported. Toxicities were mainly haematopoietic, infection, mucositis and gastro-intestinal. Severe adverse events were reported in five patients. These were:

- Septic meningitis complicating Ommaya reservoir access. Resolved
- Sepsis requiring inotropic support. Resolved
- Development of a frontal cerebral lesion (? IT therapy-related)
- Seizure after ICE and IT MTX in a patient with metastatic disease
- Radiogenic gliosis in a patient who received IT Methotrexate after RT (this is not according to guidance)

Current recommendations for treatment of ATRT

Based on current available data, we recommend using the EuRhab protocol for treatment of all patients with ATRT. Treating physicians are encouraged to register patients, and to report toxicities relating to treatment.

The full EuRhab protocol is available separately. Specific considerations for UK patients are listed below.

Diagnosis

The diagnostic criteria for ATRT are given within EuRhab. For patients within the UK, coordination of central review of pathology and molecular diagnostics is offered using the same laboratories which already participate in the UK National Medulloblastoma feasibility study. Samples should be sent to the National coordinating centre (Newcastle) and will be distributed appropriately for pathology review and molecular diagnostics from there.

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Central review of pathological specimens will be undertaken by the following pathologists:

Dr. Stephen Wharton, University of Sheffield.

Dr. Tom Jacques, Great Ormond Street Hospital, London.

Dr. Keith Robson, Queen's Medical Centre, Nottingham.

A “real-time” diagnostic service is also provided by

Professor Dr. M. Hasselblatt,
Institute for Neuropathology,
Münster, Germany.

Samples received by his laboratory will be managed and a result returned within 5 days.

Pathology review is also available through the laboratories of Professor Dr. F. Giangaspero, Institute of Neuropathology, Rome, Italy

Molecular diagnostics

It is recommended that patients registered on the EuRhab protocol will have evaluation for molecular genetics and cytogenetics. Samples sent to Newcastle will be distributed to the UK designated laboratories. Within the UK, mutation analysis must be performed in an accredited NHS service laboratory and the two national laboratories currently offering MLPA and sequencing analysis for hSNF5/ini1 are in London and Manchester as detailed below:

Dr Nicholas Lench,
Director of Molecular Genetic Diagnostic Services
Great Ormond Street Hospital
York House
Great Ormond Street
London

Dr Helena Kempski
Paediatric Malignancy Unit (PMU)
Camelia Botnar Laboratories, CBL Level 2
Great Ormond Street Hospital
Great Ormond Street
London, WC1N 3JH
Tel: 020 7828 8883 (direct line)
Email: KempsH@gosh.nhs.uk
Email: H.Kempski@ich.ucl.ac.uk

Dr Andrew Wallace
Regional Molecular Genetics Service
Genetic Medicine (6th Floor)
Manchester Academic Health Science Centre St Mary's Hospital
Oxford Road Manchester M13 9WL UK

In addition, these techniques can also be performed in the following European laboratories:

Cytogenetics

- Professor Dr. R. Siebert, Institute of Human Genetics, Kiel, Germany or
- Professor Dr. O. DeLattre, Centre de Recherche de l`Institute Curie, Paris, France

Molecular Genetics

- Professor Dr. R. Schneppenheim, Pediatric Hematology/Oncology, Hamburg, Germany
- Professor Dr. O. DeLattre, Centre de Recherche de l`Institute Curie, Paris, France

The large majority of patients will lack INI-1 expression with histopathology consistent with the diagnosis of ATRT. There are reported cases with preserved expression, and for these patients, detailed molecular genetic analysis will be of value. Such patients may be highly informative of the

process of tumour formation, and storage of tissue for analysis is particularly recommended. Similarly, there are other tumours which lack INI-1 expression but are not considered to be ATRT.

Tissue requirements for molecular diagnostics

It is recommended that frozen tissue be analysed by FISH for the SMARCB1 locus. The recommendation for tumour tissue is given within the EuRhab protocol, and is:

- **5 unstained touch preps OR**
- **5 unstained cryo-sections of the tumor (or cryo block on dry ice) OR**
- **5 unstained paraffin sections of the tumor (or paraffin block)**

Where there is a likely germ-line mutation (infants under 2 years of age or the presence of multifocal primaries, or a family history), analysis of tumour and germ line DNA should be made at the same time.

Recent data indicate that the incidence of germline mutation of the hSNF5 / ini1 locus is higher than previously recognised in AT/RT and malignant rhabdoid tumours, with an incidence in excess of 30%. Importantly, about 50% of germline hits are sequence abnormalities and 50% involve deletions. Both sequencing and MLPA (multiplex ligation-dependent probe amplification) analysis are required to avoid false negative results. It is recommended that all patients are referred for genetic counseling.

Surgical approach

Radical resection is recommended wherever possible. The degree of resection, based on SIOP recommendations using post-operative imaging and surgical findings, should be reported for all patients.

Diagnostic evaluation

Each patient should have:

- A complete medical history, to include a family history of cancer.
- Physical examination
- Weight, height and body surface area and pubertal status
- Karnofsky Performance Status (KPS) or Lansky play score
- Full blood count, serum electrolytes, liver function tests, kidney function tests)
- Measurement of GFR (this need not delay treatment)

- Urinary protein, α1-microglobulin, creatinine, phosphate, calculation of tubular resorption of phosphate (TRP) and 24 hour protein loss.
- Echocardiogram

In addition, the EuRhab protocol specifies that documentation of viral serology for hepatitis A, B and C, HIV, CMV, Parvovirus B19.

Initial Staging

Radiology

Imaging of the primary tumour by MRI scan with measurement of tumour volume. Imaging shall be according to current CCLG guidelines. In particular, whole neuraxis imaging, with T1 before and after Gadolinium, and T2 sequences shall be performed.

Spinal imaging, if not performed pre-operatively, shall be completed within 48 hours of the first surgical procedure.

Post-operative imaging shall be repeated not later than 48 hours after resection of the tumour to assess the presence of residual disease.

The EuRhab protocol specifies whole body MRI to exclude simultaneous, non-CNS tumours. This has not been adopted for other tumours, but a systematic search for other tumours should be undertaken. This may be by:

- Detailed clinical examination
- Whole body MRI, as a two stage process. Neuraxis imaging should be performed in different phases from imaging of the rest of the body, in order to avoid possible degradation of imaging to the neuraxis,

  OR
- Chest Xray and abdominal USS with particular care to image the kidneys

Central review of images is requested for all patients entered in the EuRhab registry.

CSF evaluation

CSF evaluation shall be performed not sooner than 14 days after the last operation, and preferably by lumbar puncture. Negative intra-operative CSF cytology should not be taken as evidence of lack of CSF dissemination, although the incidence of M1 disease alone is not known.

Ventricular access devices and use of shunts

CSF-delivered therapy is an important feature of this treatment protocol, and consideration to the placement of a ventricular access device should be given. Intrathecal therapy is acceptable as an alternative, but the logistics of delivering IT chemotherapy in a patient after recent neurosurgery may prevent timely administration.

Some patients will require a CSF diversion procedure because of hydrocephalus. Where this is by placement of a ventriculoperitoneal shunt, the delivery of chemotherapy to the CSF space is unlikely to be effective, and wherever possible, alternative methods of control are to be preferred. Third ventriculostomy will allow chemotherapy to be delivered without loss. Where CSF obstruction is hoped to be temporary, external ventricular drainage which can be interrupted may allow successful delivery of chemotherapy.

Venous access

All patients will require reliable, central venous access. A double lumen

Hickman line or equivalent is recommended.

Investigations prior to starting treatment

An echocardiogram shall be performed prior to the first dose of anthracycline chemotherapy and prior to each subsequent dose.

GFR evaluation should be performed before administering ICE chemotherapy. This will normally be by assessment of ^{51}Cr EDTA elimination.

Intraventricular and intrathecal chemotherapy dosing in the EuRhab protocol.

There is a significant difference in the approach proposed in EuRhab and that which is normally taken in the UK.

The recommended administration of intraventricular methotrexate in the EuRhab protocol is in four, daily doses according to age (0.5, 1 or 2mg daily x4 or X3). A total of 22 doses are given in 6 cycles, each dose to a maximum of 2mg. Max cumulative dose 44mg.

Methotrexate levels are monitored, and subsequent doses withheld if a level >5 µM is recorded.

This approach is not conventional in the UK, where single IT doses of Methotrexate are usually administered. Given that intraventricular therapy is of unproven value, and the efficacy of methotrexate itself uncertain, it is difficult to insist on this approach.

When considering absolute doses of MTX, comparison with other chemotherapy regimes may be of value.

- In the DFCI study reported by Chi et al, at least 11 doses of methotrexate are administered at doses up to 15 mg, a cumulative dose of 165 mg. One patient developed radiation recall in this study.
- In the MUV (Vienna) protocol, which is particularly intensive with regard to IT therapy, patients receive 9 courses of IT MTX, with 27 doses each to a maximum of 2mg. Total cumulative dose 54 mg, with, in addition, 45 doses of etoposide, 0.5mg (cumulative dose 22.5 mg) and 9 doses of Depocyte 35mg (cumulative dose 315 mg).
- Patients treated for B-Non-Hodgkin Lymhoma (Group C) receive 10 intrathecal doses of methotrexate at a dose of 8/10/12/15 mg according to age. A cumulative dose of 150 mg might be received. These patients would not normally undergo irradiation.
- If the fractionated dose with each cycle of Dox, ICE or VCA is replaced by a single dose according to the B-NHL age-related guidance, patients would receive 6 doses, each with a maximum 15mg. Max cumulative dose 90 mg.

The EuRhab recommendations appear cautious, but there was one patient reported with radiogenic gliosis in the first group of 47 patients. This patient received IT MTX after radiation.

The EuRhab protocol also recommends monitoring of methotrexate levels and prompt action to enhance elimination if this exceeds 5mM after 48 hours. This

has not been a feature of management in the UK.

Recommendation:

At the present time, it is recommended that methotrexate be administered as a single dose intrathecally or intraventricularly. Doses should be according to previously established safe practice in leukaemia, according to age.

Intraventricular therapy should be discontinued in all patients at the start of radiotherapy.

No CSF-directed chemotherapy will be given after RT.

Evaluation of response

MRI is recommended after 2, 4, 6 cycles and after the end of treatment. For those patients over the age of 18 months, or if early tumour progression is seen, radiotherapy will be indicated early: MRI should be performed prior to RT and 6 weeks following completion. Chemotherapy to a maximum of nine cycles should continue, and MRI examinaton performed after each alternate cycle.

Radiotherapy

Radiotherapy is advised for most patients. For those over 18 months of age, this should be at the earliest opportunity. In those with metastatic disease, it should be delayed until after the intensive phase of chemotherapy. For infants under the age of 18 months, RT is generally not recommended, although for some, RT can be delayed until the patient has reached this age. The primary tumour dose will be 54.0 Gy PTV given as 5 fractions of 1.8 Gy per week, according to ICRU 50/62.

Patients with metastatic disease shall receive a CSI dose of 24 Gy CSRT (age 18-36 m), or 35.2 Gy (age >36m). The use of protons may be considered.

Note that intraventricular or intrathecal therapy will be discontinued as soon as radiotherapy has begun and will not be re-started.

High dose chemotherapy may be used as an alternative to radiotherapy. The administration of both high dose and radiation therapy is not recommended.

Proton Beam Radiotherapy

The use of protons is limited in the UK, but patients with ATRT do fall into a group who may benefit from this approach. It is recommended that proton beam therapy is discussed for each patient. Discussions are in progress concerning the possible designation for funding purposes of ATRT using proton beam therapy.

High dose chemotherapy

This is an alternative to radiotherapy to be considered for those patients

where anticipated morbidity (principally in terms of neuro-developmental outcome) of radiation therapy is deemed too severe. The decision to omit radiation therapy must be taken by the treating clinician, but the patients for whom this may be appropriate may include infants with a large supra-tentorial tumour, for whom extensive irradiation of cerebral cortex would be required. Patients with posterior fossa tumours should normally receive focal irradiation.

The choice of high dose therapy is not mandated, but a recommended regime using Carboplatin and ThioTEPA is provided.

APPENDIX 1

CCLG BRAIN TUMOUR IMAGING PROTOCOL

(26)
January 2009

It is essential that all new children's brain tumour cases are imaged using a consistent and comprehensive protocol. This is to ensure that optimal diagnostic information can be obtained, consistency is maintained, studies are directly comparable and that all brain tumour cases can be recruited into national CCLG driven tumour studies. It is equally important that follow up imaging is undertaken in a consistent and timely manner. Lack of a consistent protocol has lead to very significant difficulties in analysing imaging of patients enrolled into CCLG tumour studies from different centres in the UK.

In future, lack of adherence to the national CCLG imaging protocol will exclude new cases being recruited to CCLG studies. The protocol given below is based upon the imaging protocol published in 2001[1] but reflects recent advances in imaging techniques (DTI, perfusion MRI, MRS). Not all centres can or will wish to use these newer techniques, and therefore these are given as optional sequences. Many centres will have their own preferred imaging sequences and this protocol is not intended to be proscriptive or to exclude other sequences and techniques, however it is essential that a standardised basic set of sequences is adopted nationally.

NEW CASES:

BRAIN

Standard sequences
Axial T1, T2
Coronal FLAIR
DTI and/or DWI (with ADC maps)
Post Gd Ax, Cor, Sag T1: at 1.5T
Post Gd Ax T1, Ax 3D T1 volume: at 3T

Optional sequences (according to local capacity/availability or CCLG trial involvement)
Cor/SagT2 or FLAIR
Perfusion MRI (requires placement of blue or pink cannula)
ASL
MRS

SPINE

Standard sequences
Sag T1 (post Gd)
Ax T1 through any equivocal focal abnormality

Optional:

Sag T2

IMMEDIATE POST OP (WITHIN 24 HOURS)

BRAIN
Standard sequences
Ax T1, T2,
Coronal FLAIR
DTI and/or DWI (with ADC maps)
Post Gd Ax, Cor, Sag T1: at 1.5T
Post Gd Ax T1, Ax 3D T1 volume: at 3T

SPINE (only if not obtained prior to surgery)
Standard sequences
Sag T1
Ax T1 through any equivocal focal abnormality

FOLLOW UP EXAMINATIONS

BRAIN

Standard sequences
Axial T1, T2
Coronal FLAIR
DTI and/or DWI (with ADC maps)
Post Gd Ax, Cor, Sag T1: at 1.5T
Post Gd Ax T1, Ax 3D T1 volume: at 3T

Optional *(according to local preference or CCLG trial involvement)*
Cor/Sag T2 or FLAIR
Perfusion MRI (requires placement of blue or pink cannula)
ASL
MRS if tumour size >1.0cm (and dependent on tumour type/protocol)

SPINE (dependent on tumour type/protocol)
Standard sequences
Sag T1, (post Gd)
Ax T1 through any equivocal focal abnormality
Optional Sag T2

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