EUROPEAN JOURNAL OF CANCER 48 (2012) 353–359

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Central nervous system atypical teratoid rhabdoid tumours: The Canadian Paediatric Brain Tumour Consortium experience

L. Lafay-Cousin [a,*], C. Hawkins [b], A.S. Carret [c], D. Johnston [d], S. Zelcer [e], B. Wilson [f], N. Jabado [g], K. Scheinemann [h], D. Eisenstat [i], C. Fryer [j], A. Fleming [j], C. Mpofu [k], V. Larouche [l], D. Strother [a], E. Bouffet [m], A. Huang [m]

[a] Division of Pediatric Hematology Oncology and Bone Marrow Transplantation, Alberta Children's Hospital, Calgary, Alberta, Canada
[b] Department of Pediatric Pathology, Hospital for Sick Children, Toronto, Ontario, Canada
[c] Division of Pediatric Hematology Oncology, Hospital Sainte Justine, Montreal, Quebec, Canada
[d] Division of Pediatric Hematology Oncology, Children Hospital of Eastern Ontario, Ontario, Canada
[e] Division of Pediatric Hematology Oncology, Children Hospital of Western Ontario, London, Ontario, Canada
[f] Division of Pediatric Hematology Oncology, Strollery Children's Hospital, Edmonton, Alberta, Canada
[g] Division of Pediatric Hematology Oncology, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada
[h] Division of Pediatric Hematology Oncology, McMaster University, Hamilton, Ontario, Canada
[i] Division of Pediatric Hematology Oncology, Cancer Care Manitoba, Winnipeg, Manitoba, Canada
[j] Division of Pediatric Hematology Oncology, Children and Women British Columbia's Hospital, Vancouver, British Columbia, Canada
[k] Division of Pediatric Hematology Oncology, Saskatoon Cancer Center, Saskatoon, Saskatchewan, Canada
[l] Division of Pediatric Hematology Oncology, Hospital Universitaire de Quebec, Quebec City, Quebec, Canada
[m] Pediatric Brain Tumor Program, Hospital for Sick Children, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 12 May 2011
Received in revised form 2 August 2011
Accepted 12 September 2011
Available online 22 October 2011

Keywords:
Atypical teratoid rhabdoid tumor
CNS
Paediatric
Population based study
High dose chemotherapy
Radiation therapy

ABSTRACT

Background: Atypical teratoid rhabdoid tumours (ATRT) are aggressive brain tumours mostly occurring in early childhood. Largest published series arise from registries and institutional experiences (1–4). The aim of this report is to provide population-based data to further characterise this rare entity and to delineate prognostic factors.

Patients and methods: A national retrospective study of children ⩽18 years diagnosed with a central nervous system (CNS) ATRT between 1995 and 2007 was undertaken. All cases underwent central pathology review.

Results: There were 50 patients (31 males; median age at diagnosis of 16.7 months). Twelve patients were >36 months. Infratentorial location accounted for 52% of all cases. Nineteen patients (38%) had metastatic disease. Fifteen (30%) underwent gross total resection (GTR). Ten patients (20%) underwent palliation. Among the 40 remaining patients, 22 received conventional chemotherapy and 18 received high dose chemotherapy regimens (HDC); nine received intrathecal chemotherapy and 15 received adjuvant radiation.

Thirty of the 40 treated patients relapsed/progressed at a median time of 5.5 months (0–32). The median survival time of the entire cohort was 13.5 months (1–117.5 months).

* *Corresponding author:* Address: Division of Pediatric Hematology Oncology and Bone Marrow Transplantation, Alberta Children's Hospital, 2888 Shaganappi trail NW, Calgary, Alberta, Canada. Tel.: +1 403 955 2554; fax: +1 403 955 2645.
E-mail address: lucie.lafay-cousin@albertshealthservices.ca (L. Lafay-Cousin).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.09.005

Age, tumour location and metastatic status were not prognostic. Patients with GTR had a better survival (2 years overall survival (OS): 60% ± 12.6 versus 21.7% ± 8.5, $p = 0.03$). HDC conferred better outcome (2 years OS 47.9% ± 12.1 versus 27.3% ± 9.5, $p = 0.036$). Upfront radiation did not provide survival benefit. Six of the 12 survivors (50%) did not receive radiation.

Conclusion: The outcome of CNS ATRT remains poor. However, the use of HDC provides encouraging results. GTR is a significant prognostic factor. The role of adjuvant radiation remains unclear.

1. Introduction

Since their first description in the mid 1980s, atypical teratoid rhabdoid tumours (ATRT) of the central nervous system (CNS) are increasingly recognised and are now routinely diagnosed despite their rarity.[5–7] These brain tumours that mostly affect infants and young children have historically been characterised by an aggressive behaviour and a grim prognosis with a median survival ranging from 6 to 11 months.[3,8,9] Given the rarity of the disease, our current knowledge is mostly based on small series with a limited number of patients. No definitive guidelines have been established that reflect optimal treatment. Most recent treatment strategies recommend maximal surgical resection followed by intensive chemotherapy with or without intrathecal chemotherapy and focal or craniospinal radiation. Although early results of pilot studies have shown encouraging results, the respective contribution of each modality in improved outcome is unclear. In the past 5 years treatment approaches in Canada have been relatively homogeneous and based on the use of high dose chemotherapy. The use of adjuvant radiation from centre with an even distribution of children subjected or not to radiation. With this large centrally reviewed national cohort, our aim was to provide population-based data on this entity to better define prognostic factors and highlight new trend in outcome.

2. Patients and methods

2.1. Patients

This retrospective study was conducted through the Canadian Paediatric Brain Tumour Consortium (CPBTC), a network of 17 Canadian Paediatric centres collaborating in paediatric neuro-oncology research. After approval from their respective institutional review board, each participating centre was asked to provide anonymised clinical data and pathology tumour slides on patients, aged between 0 and 18 years, and locally diagnosed with CNS ATRT between 1995 and 2007. Data collection forms inquired about demographics, pathology and cytogenetic reports, surgical procedures, post operative management and outcome.

2.2. Central pathology review

All cases underwent central pathology review (CH) including immunostaining for INI1/BAF47 to confirm the diagnosis of AT/RT. For immunohistochemistry representative four micrometre sections were cut from each case and mounted on positively charged microscope slides. INI1 (BAF47, BD Biosciences, Mississauga, Canada) immunohistochemistry at a dilution of 1:100 was performed on the Ventana Benchmark XT autoimmunostainer (Ventana Medical Systems, Tucson, AZ), with a closed avidin–biotin complex method system using the Ultraview reagent kit (Ventana Medical Systems, Tucson, AZ). Neuroblastoma was used as a positive control. Further, for a tumour to be considered true negative on-slide endothelial cells must have been immunopositive. Parallel slides omitting the primary antibody were run as a negative control in all cases.

Data capture was completed in May 2010 and central pathology review in September 2010.

2.3. Statistical analysis

The statistical analysis was performed using SPSP15. For descriptive statistics, continuous data were compared using Student's *t*-test. Non-continuous data were compared using Chi-square. For both tests $p < 0.05$ was considered significant. Estimation of event-free survival and overall survival was performed using the Kaplan–Meier analysis and significance testing ($\alpha = 0.05$) based on the log-rank test. Overall survival was calculated from the date of diagnosis to the date of last follow-up or date of death from any cause. Event-free survival was calculated from the date of initial diagnosis to the date of earliest radiologic disease progression. The level of significance was $p = 0.05$.

3. Results

Among the 17 institutions of the CPBTC, 6 had no patients eligible for the study. Data were obtained from 10 out 11 remaining centres.

3.1. Patients description

Clinical information was obtained on 55 patients with an institutional diagnosis of CNS ATRT. Samples for pathology review were available for 53 patients. Seven samples previously reviewed in the context of a retrospective institutional study were not revaluated for the purpose of the current report.[10] Following central review, five patients were excluded from the initial cohort as the diagnosis of AT/RT was not confirmed. The two patients without sample available for central review were kept in the final cohort after careful review of the institutional pathology and cytogenetic reports describing morphological characteristics, cytogenetic alterations and immunohistochemical profiles in keeping with ATRT. Results

Table 1 – Patient characteristics.

	N = 50
Sex ratio	31 M/19 F
Median age at diagnosis	16.7 months (1–187.9)
<12 months	17 (34%)
>36 months	12 (24%)
Metastatic status at diagnosis	19 (38%)
M1	5
M2	3
M3	4
M2/M3	4
M4, M4/MRT	3
Extent of resection	
GTR	15 30%)
STR	18 (36%)
PR	14 (28%)
Biopsy	3 (6%)
Palliative care	10 (20%)
Conventional chemotherapy	22 (55%)
HDC	18 (45%)
IT chemotherapy	9 (22.5%)
Radiation	21 (52%)
CSI	11
Focal	9
Cranial	1
Adjuvant RT	15 (37.5%)

M, male; F, female; MRT, multiple rhabdoid tumours; GTR, gross total resection; STR, subtotal resection; PR, partial resection; HDC, high dose chemotherapy; IT, intrathecal chemotherapy; RT, radiotherapy; CSI, craniospinal irradiation.

are therefore reported on a cohort of 50 patients (Table 1). Amongst these, 31 were males (62%). The median age at diagnosis was 16.7 months (range 1 day–15.6 years). Twelve patients (24%) were older than 36 months. The median duration of presenting symptoms was 3 weeks (range 0–20 weeks). Most frequent presenting symptoms were signs related to increased intracranial pressure, followed by change in behaviour (irritability, regression of milestones) as well as localising signs like motor deficit, cranial nerve deficit and seizure. Complete staging consisting of magnetic resonance imaging (MRI) of the spine and brain and cerebrospinal fluid (CSF) cytology from lumbar puncture, was available for 39 patients (78%). Nineteen patients had metastatic disease at diagnosis (Table 1). Three patients presented with metastasis or lesion outside of the CNS; one had positive uptake on the vault on bone scan, and a positive submandibular lymph node on biopsy. Two others presented with synchronous rhabdoid lesions (brain + kidney and brain + skin, lung, bone) in keeping with multiple rhabdoid tumours syndrome (MRT); nine patients (18%) underwent genetic testing and three were found to carry germline mutation for INI1.

Twenty-six (52%) tumours were infratentorial, 22 were supratentorial (44%) and two were intraspinal (4%). Initial maximal surgical resection was attempted in all but three patients who only had biopsy. Two patients underwent second-look surgery that resulted in gross total resection (GTR) and subtotal resection (STR), respectively. Overall, gross total resection was achieved in 15 patients (30%).

Following surgical resection, ten patients (20%) received no further anti-tumour therapy. These patients who underwent palliative care immediately after diagnosis were younger (median 7.6 months [range 1.5–21.4] compared to 19.5 months [range 0–188] for patients who received active postoperative treatment). However, both groups had similar metastatic distribution (40% versus 37.5%) (See Table 2).

3.2. *Survival and prognostic factors*

Survival data are given for the 40 patients who received active post-operative treatment.

Thirty patients either relapsed or progressed at a median time of 5.5 months from diagnosis (range 0–32 months). Only three patients relapsed beyond 12 months from diagnosis. None of the relapse occurred outside of the Collin's Law period. The median survival time was 14 months with a projected 2-years overall survival of 36.4% ± 7.7. At the completion of survey, 12 patients were alive at a median follow up of 43 months (range 10–117.3 months).

3.3. *Age and demographics*

Median survival time according to age was, respectively, 9.6 months for patients <12 months of age ($n = 9$), 17.4 months for patients 12–36 months ($n = 19$) and 19.1 months for those >36 months ($n = 12$). There was a trend towards a poorer outcome for children younger than 12 months, however this did not reach statistical significance ($p = 0.06$) (Fig. 1a).

Sex ($p = 0.67$), metastatic status at diagnosis ($p = 0.24$) and tumour location ($p = 0.49$) were not associated with significant difference in outcome.

3.4. *Extent of surgery*

Twelve patients (30%) had a gross total surgical resection. Patient who achieved a GTR had a better survival with a 2y OS of 60% ± 12.6 compared to 21.7% ± 8.5 for patients who underwent less than GTR ($p = 0.03$) (Fig. 1b).

3.5. *Chemotherapy*

Twenty-two patients (55%) received conventional chemotherapy and 18 (45%) received a protocol that included high dose chemotherapy and autologous stem cell rescue (HDC and SCR). Various regimens of conventional chemotherapy were used, essentially 'baby brain protocols'[11] IRS III like[12] and ICE regimens[13]. Only nine patients received anthracycline based chemotherapy regimens.

Three major high dose chemotherapy regimens were used: the Headstart regimen[14] (methotrexate based induction followed by one cycle of high dose Carboplatin Thiotepa, VP16) in four patients, three sequential cycle of high dose Carboplatin and Thiotepa in seven patients whilst seven patients received a methotrexate based induction followed by three sequential high dose Carboplatin and Thiotepa.

Nine of the 18 patients who received HDC regimens were alive at a median follow up time of 40.8 months (10–90) from diagnosis. HDC was associated with a significant survival

Table 2 – Characteristics and treatment of the survivors.

No	Sex/age at diagnosis	Tumour location	Metastatic status	Surgery	Conventional CT only	CT regimen including high dose chemotherapy (HDC)	Intrathecal chemotherapy (IT)	RT field and dose	RT indication	Relapse or progression	FU from diagnosis (months)
1	F/19.1	Supra tentorial	M2/M3	GTR	VCR, VP16, CB, IFOS	–	–	45 Gy cranial/780 focal	Relapse	+	117.3
2	M/12.5	Supra tentorial	M0	GTR	–	MTX, CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	–	–		–	33.5
3	F/131.5	Supra tentorial	M0	GTR	VCR CCNU PRED	–	–	59 Gy focal	Primary	–	84.0
4	F/17	Infra tentorial	M0	GTR	–	CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	–	–		–	96.0
5	M/15.2	Infra tentorial	M0	STR	–	CDDP, CPM, VCR, TMD VP16 (CB Thiotepa VP16) × 1	–	–		–	55.5
6	M/60.7	Infra tentorial	M1	PR	–	MTX, CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	–	36 Gy CSI/18 Gy focal boost	Primary	–	10.0
7	F/19.8	Supra tentorial	M0	GTR	–	MTX, CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	–	55.8 Gy Focal	Primary	–	40.8
8	M/180.4	Supra tentorial	M0	GTR	IFOS, CB, VP16	–	–	36 Gy CSI/18 Gy focal boost	Primary	–	114.8
9	F/11.2	Infra tentorial	M2	STR	–	CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	TIT × 2	–		–	42.7
10	M/31	Infra tentorial	M0	GTR	–	CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	TIT × 2	54 Gy focal	Primary	–	43.4
11	M/43.3	Supra tentorial	M0	GTR	–	CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	TIT × 3	–		–	29.2
12	M/28.2	Supra tentorial	M2	STR	–	CDDP, CPM, VCR, VP16, (CB, Thiotepa) × 3	TIT × 3	–		Persistent CSF+[a]	23.5

F, female; M, male; GTR, gross total resection; STR, subtotal resection; PR, partial resection; VCR, vincristine; CCNU, Lomustine; CB, carboplatin; CDDP, cisplatinum; CPM, cyclophosphamide; TMD, temozolomide; VP16, etoposide; TIT, triple intrathecal (aracytine, hydrocortisone, methotrexate); CSI, craniospinal irradiation; Gy, Gray; IFOS, ifosfamide; PRED, prednisone; RT, radiation therapy; MTX, methotrexate.

a Treated with tamoxifen and Cis retinoic acid.

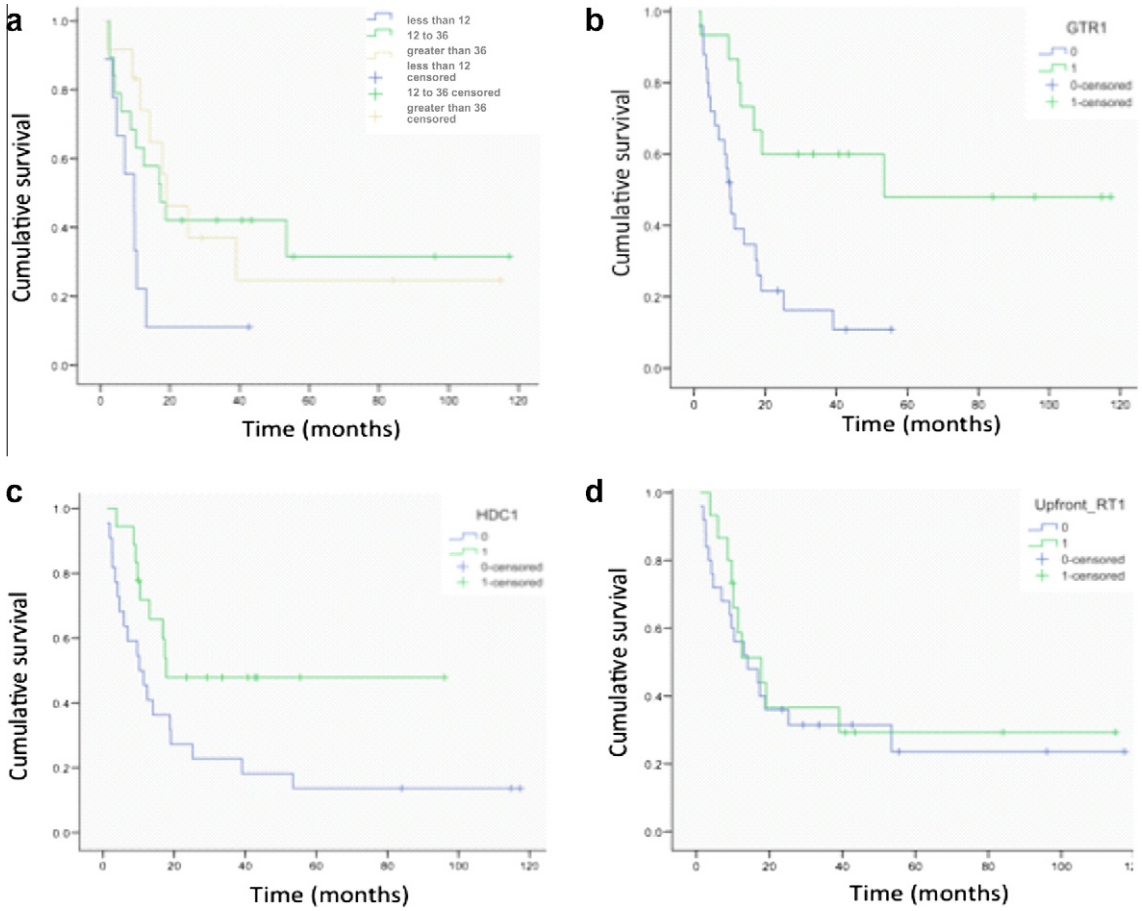

Fig. 1 – Analysis of overall survival (Kaplan–Meier method) according to: (a) age at diagnosis; (b) the extent of resection; (c) the use of high dose chemotherapy; (d) the use of adjuvant radiation.

benefit with a 2 years OS of 47.9% ± 12.1 versus 27.3% ± 9.5 for the conventional chemotherapy group ($p = 0.036$) (Fig. 1c).

In addition to systemic therapy, nine patients (22.5%) received intrathecal chemotherapy (IT). Among them, six were treated with systemic HDC. The most commonly used IT drugs were the triple combination of cytosine arabinoside, hydrocortisone and methotrexate (seven patients) or single agent Thiotepa (two patients) with a median of 3 IT administrations [range 1–10] per patients during therapy. The used of IT chemotherapy was not associated with a significant prognostic value (median survival of 17.8 months versus 13.1 months ($p = 0.32$).

3.6. *Radiation*

Twenty-one (52.5%) patients received radiation therapy during therapy (11 craniospinal radiation with focal boost, nine focal radiation, one cranial radiation). The dose of craniospinal radiation ranged from 12 to 45 Gy (median 36 Gy) with the boost dose to the primary tumour ranged from 11 to 33 Gy. For the patient who received focal radiation, the dose of focal radiation ranged from 45 to 59 Gy (median 54 Gy). Radiation therapy was delivered in an adjuvant setting in 15 children and at the time of relapse or progression in the six remaining children. The median age at diagnosis of patients who received RT was 34 months (6.3–187.9) as compared to 14 months (0–43.3) for those who did not. Whether radiation was given in an adjuvant setting or at any time during therapy, did not appear to significantly influence survival. Patient who received radiation in an adjuvant setting had a median survival of 17.8 months as compared to 14 months for those who did not ($p = 0.64$) (Fig. 1d).

Eleven of the 18 patients treated with HDC (39%) did not receive adjuvant radiation. Median survival time has not been reached yet for these 11 patients: at the completion of the survey, six were alive at a median follow up of 38.1 months (range 23.5–96). Three of the seven children who received RT with HDC were alive (10, 40.8, 43.4 months). In total six of the 12 survivors (50%) did not receive radiation.

Among the 12 survivors, 10 were alive in first complete remission whilst two were in second complete remission.

4. Discussion

This national registry represents one of the largest population-based series of CNS ATRT reported to date. The central pathology review ensured the homogeneity of this retrospective series. Although we collected cases from 1995 onwards, a period during which this entity was better recognised, it is likely that our survey underestimated the total number of Canadian CNS ATRT, since the central pathology review did not include all embryonal tumours diagnosed during the study.[2,10]

Unlike voluntary based registry[1] or series from clinical trials, this population-based registry provides unbiased data with regard to demographic characteristics and post operative management. The median age at diagnosis (16.7 months) of our population appears to be younger than what was reported in the United States of America (USA) CNS ATRT registry or in recent clinical trials[1,3,4] but more in keeping with the ATRT population from the recently reported Austrian registry.[2] In our series, 20% of the patients did not receive further therapy beyond surgery. This is in keeping with the initial descriptions from Rorke et al.[15] where 14% of the patients did not receive any postoperative treatment. Children who underwent post operative palliative care tended to be younger at presentation. The inclusion of untreated younger patients may contribute to explain the lower median age at diagnosis. Although the number of CNS ATRT cases per year continuously increased from 1995 to 2007, the proportion of untreated patients remained constant throughout the study period. This information is important and suggests that registries are an important complement of prospective protocols as they allow incorporating these missing patients.

In our study, we confirmed a rate of metastatic disease in the range of 30–40% and we did not find a prognostic significance of dissemination at diagnosis. In contrast with previous reports, we did not find a survival advantage in children older than 3 years.[1,4]

Despite the known prognostic value of complete resection, that was confirmed in our experience, only two children underwent second look surgery to attempt gross total resection.[1,3,4] It should be reinforced that second look surgery should be strongly considered as recommended in most current ATRT protocols.

The management of CNS ATRT with conventional chemotherapy has been consistently associated with dismal outcome and most series have supported the benefit of aggressive multimodal therapy.[16] Chi et al.[3] recently reported on 20 patients a 2 years progression free and overall survival of 53% ± 13 and 70% ± 10, respectively, with a protocol using intensive rhabdomyosarcoma-based chemotherapy, intrathecal therapy and age-based radiotherapy. Similarly from the 19 patients in the Austrian registry, all eight long term survivors received combined multimodality therapy, with high dose chemotherapy in seven patients, intrathecal therapy in 6 and all received focal radiation.[2]

The respective role of each treatment modality, namely high dose chemotherapy, intrathecal chemotherapy and radiation, remains difficult to delineate.[17] Our series provide further evidence that high dose chemotherapy is associated with survival benefit when compared to conventional therapy with a 2 years OS of 47.9% ± 12.1 versus 27.3% ± 9.5 ($p = 0.036$).[18,19] Whether IT chemotherapy contributes to improved outcome or can replace craniospinal radiation still remains to be confirmed. In their meta-analysis Athale et al. suggested patients who received IT therapy had a survival advantage with a 2 years OS of 64% versus 17.3% for those who did not ($p < 0.0001$).[20] In our series, the use of IT was only described in most recent patients but in only nine patients, limiting our ability to draw meaningful conclusion.

Similarly, based on the initial experience of IRS III type therapy in rhabdoid tumour,[12] some authors have suggested a role for anthracyclines in CNS ATRT.[21–23,3] In our experience nine patients received an anthracycline based regimen but none of them are long term survivors.

The potential contribution of radiation in this subtype of tumour is even more a matter of debate since 2/3 of the patients diagnosed with ATRT are younger than three at the time of diagnosis and therefore more vulnerable to radiation induced neurocognitive impairment. Several reports have suggested a survival benefit with radiotherapy.[24,25] Although in the ATRT registry, the median age of 13 patients who received upfront radiation was higher (47 months) compared to the entire cohort (24 months),[1] it is possible that confounding factors such as age or the addition of multimodal therapies contributed to that figure. Based on these findings and those from the NCI ATRT workshop,[8] radiation has been recommended and integrated into current ATRT protocols.

We did not find any prognostic value for radiation neither when used in an upfront setting nor when delivered at any given time during the course of the disease. The absence of significant value may be due to the limited small size of our cohort. However six out of the 11 long term survivors in our experience were treated with HDC without radiation (median follow up of 38.1 months (range 23.5–96). In total six of 12 survivors (50%) did not receive radiation. These encouraging results suggest that some patients with ATRT may be spared from radiation. Amongst these six patients, two had metastatic disease at diagnosis and two had a subtotal resection of their mass. Further identification of molecular markers may help to better delineate the subgroup of patients that can be cured without radiation.

5. Conclusion

Despite the well recognised dismal prognosis associated with CNS ATRT, a trend to improved outcome is emerging with the use of multimodalities strategies and the data from our national cohort to support that trend. Furthermore our series highlights the encouraging results associated with the use of high dose chemotherapy and describe a proportion of long term survivors (50%) who did not receive radiation.

Conflict of interest statement

None declared.

Acknowledgements

This work has been supported by a research grant from B.R.A.I.N. Child (Brain Tumor Research Assistance and information Network).

REFERENCES

1. Hilden JM, Meerbaum S, Burger P, et al. Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry. *J Clin Oncol* 2004;**22**(14):2877–84.

2. Woehrer A, Slavc I, Waldhoer T, et al. Incidence of atypical teratoid/rhabdoid tumors in children: a population-based study by the Austrian Brain Tumor Registry, 1996–2006. *Cancer* 2010.
3. Chi SN, Zimmerman MA, Yao X, et al. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. *J Clin Oncol* 2009;**27**(3):385–9.
4. Tekautz TM, Fuller CE, Blaney S, et al. Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. *J Clin Oncol* 2005;**23**(7):1491–9.
5. Biggs PJ, Garen PD, Powers JM, Garvin AJ. Malignant rhabdoid tumor of the central nervous system. *Hum Pathol.* 1987;**18**(4):332–7.
6. Rorke LB, Packer R, Biegel J. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood. *J Neurooncol* 1995;**24**(1):21–8.
7. Burger PC, Yu IT, Tihan T, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: a highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: a Pediatric Oncology Group study. *Am J Surg Pathol* 1998;**22**(9):1083–92.
8. Packer RJ, Biegel JA, Blaney S, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. *J Pediatr Hematol Oncol* 2002;**24**(5):337–42.
9. Strother D. Atypical teratoid rhabdoid tumors of childhood: diagnosis, treatment and challenges. *Expert Rev Anticancer Ther* 2005;**5**(5):907–15.
10. Fleming A. Redefining inidence, outcome and prognostic factors in CNS atypical teratoid rhabdoid tumors at BC children's hospital. *Neuro Oncol* 2010;**12**(6):65.
11. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. *J Clin Oncol* 2005;**23**(30):7621–31.
12. Olson TA, Bayar E, Kosnik E, et al. Successful treatment of disseminated central nervous system malignant rhabdoid tumor. *J Pediatr Hematol Oncol* 1995;**17**(1):71–5.
13. Lafay-Cousin L, Mabbott DJ, Halliday W, et al. Use of ifosfamide, carboplatin, and etoposide chemotherapy in choroid plexus carcinoma. *J Neurosurg Pediatr* 2010;**5**(6):615–21.
14. Gardner SL, Asgharzadeh S, Green A, et al. Intensive induction chemotherapy followed by high dose chemotherapy with autologous hematopoietic progenitor cell rescue in young children newly diagnosed with central nervous system atypical teratoid rhabdoid tumors. *Pediatr Blood Cancer* 2008;**51**(2):235–40.
15. Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. *J Neurosurg* 1996;**85**(1):56–65.
16. Reddy AT. Atypical teratoid/rhabdoid tumors of the central nervous system. *J Neurooncol* 2005;**75**(3):309–13.
17. Garre ML, Tekautz T. Role of high-dose chemotherapy (HDCT) in treatment of atypical teratoid/rhabdoid tumors (AT/RTs). *Pediatr Blood Cancer* 2010;**54**(4):647–8.
18. Finkelstein-Shechter T, Gassas A, Mabbott D, et al. Atypical teratoid or rhabdoid tumors: improved outcome with high-dose chemotherapy. *J Pediatr Hematol Oncol* 2010;**32**(5):e182–186.
19. Nicolaides T, Tihan T, Horn B, et al. High-dose chemotherapy and autologous stem cell rescue for atypical teratoid/rhabdoid tumor of the central nervous system. *J Neurooncol* 2010;**98**(1):117–23.
20. Athale UH, Duckworth J, Odame I, Barr R. Childhood atypical teratoid rhabdoid tumor of the central nervous system: a meta-analysis of observational studies. *J Pediatr Hematol Oncol* 2009;**31**(9):651–63.
21. Ronghe MD, Moss TH, Lowis SP. Treatment of CNS malignant rhabdoid tumors. *Pediatr Blood Cancer* 2004;**42**(3):254–60.
22. Zimmerman MA, Goumnerova LC, Proctor M, et al. Continuous remission of newly diagnosed and relapsed central nervous system atypical teratoid/rhabdoid tumor. *J Neurooncol* 2005;**72**(1):77–84.
23. Weinblatt M, Kochen J. Rhabdoid tumor of the central nervous system. *Med Pediatr Oncol* 1992;**20**(3):258.
24. Chen YW, Wong TT, Ho DM, et al. Impact of radiotherapy for pediatric CNS atypical teratoid/rhabdoid tumor (single institute experience). *Int J Radiat Oncol Biol Phys* 2006;**64**(4):1038–43.
25. Squire SE, Chan MD, Marcus KJ. Atypical teratoid/rhabdoid tumor: the controversy behind radiation therapy. *J Neurooncol* 2007;**81**(1):97–111.