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