The importance of radiotherapy in paediatric atypical teratoid rhabdoid tumour of the brain

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SUMMARY

BACKGROUND: Atypical teratoid rhabdoid tumours (ATRT) are very rare children's cancers. Approximately 200 cases of ATRT located in the central nervous system have been described in the literature up till now.

AIM: The aim of this report was to analyze the results of treatment of 8 children with these very rare neoplasms of the central nervous system, who were treated according to the Polish Paediatric Brain Tumour Group protocol.

MATERIAL AND METHODS: Eight children aged from 4 months to 22 years, 5 girls, 3 boys with ATRT of the central nervous system are presented. All children have been operated on and received multidrug chemotherapy; 5 children received radiotherapy as well. In all craniospinal irradiation was applied, in doses of 35 Gy to the whole axis and 55 Gy to tumour boost.

RESULTS: Five patients died and 3 children are still alive. The progression-free survival of all 8 patients was 3 to 73 months. The overall survival was 5 to 73 months. All living children received radiotherapy. Two of them had total surgical resection and one partial.

CONCLUSIONS: We conclude that radiotherapy prolonged survival in ATRT and should be incorporated in all treatment protocols for patients with this diagnosis.

KEY WORDS: atypical teratoid rhabdoid tumour, children, radiotherapy

Received: 20.01.2009
Accepted: 28.04.2009
Subject: original paper

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BACKGROUND

Atypical teratoid rhabdoid tumours (ATRT) are very rare children's cancers. They were described by Beckwith in 1978 as malignant rhabdoid tumours located in the kidney [1]. Cerebral location was acknowledged in the late 1980s. To date, approximately 200 cases of atypical teratoid/rhabdoid tumours of the central nervous system have been described in the literature [2]. Although ATRT accounts for less than 5% of all paediatric CNS tumours, up to 20% of malignant brain tumours diagnosed in patients less than 3 years old are ATRTs. In adults this tumour was reported anecdotally [3,4]. The cerebral form of ATRT has been mistaken for PNET/medulloblastoma tumours. There are many publications about diagnostic difficulties, especially for pathologists, when differentiating between PNET/medulloblastoma and ATRT [5, 6, 7]. These tumours have also been mistaken for ependymomas. Despite immunohistochemical and genetic testing it is very difficult to find differences between ATRT and PNET, especially in infratentorial location [8, 9, 10, 11, 12, 13]. This distinction is important, because survival times in ATRT are much shorter than those obtained for medulloblastoma/PNETs, and a significant portion of patients die as a result of local or craniospinal recurrence despite aggressive surgery and chemotherapy. There are no treatment standards

for ATRT because of their rarity, but there is some evidence that long-term survival can occur with the use of adjuvant radiation therapy [2, 14, 15].

AIM

The aim of our study is to present clinical status and treatment approaches in 8 patients with ATRT, treated according to the Polish Paediatric Brain Tumours Group protocol.

MATERIALS AND METHODS

Between 2000 and 2008, 8 children with ATRT aged from 4 months to 22 years were treated according to the Polish Paediatric Brain Tumours Group protocol [16, 17]. There were 5 girls and 3 boys. In 8 patients final histopathological diagnosis of ATRT was confirmed.

Diagnostic difficulties concerning histopathology were confirmed in 3 patients. In 2 children the tumour samples had histological features similar to PNET. However, results were uncertain and further examinations of the tumour tissue were performed, which finally confirmed ATRT. One child had a tumour with a pathological tissue image typical for medulloblastoma. He was reoperated again because of disease progression during chemotherapy. The tissue specimen obtained during the surgery was typical for ATRT. In these patients immunohistochemical data for INI-1 were not obtained.

In 2 children tumours were located in the posterior fossa region and 6 patients had supratentorial location. All children received radical treatment including surgery: 3 patients underwent total surgery, 3 subtotal and 2 partial resection. Multidrug chemotherapy was introduced as part of their treatment for all 8 patients. Three children received multidrug chemotherapy according to the Polish protocol for children below 3 years old (vincristine, etoposide, cisplatin, cyclophosphamide). In 5 patients chemotherapy was given according to the standard Polish protocol for medulloblastoma/PNET (vincristine, etoposide, carboplatin, ifosfamide, cisplatin).

Five children received radiotherapy; in all craniospinal irradiation was applied, in doses of 35 Gy to the whole axis and 55 Gy to tumour boost. This method was similar to that applied to medulloblastoma patients [18].

Three patients did not receive radiotherapy at all. In two cases progression during chemotherapy was observed, and one child was too young for radiotherapy.

RESULTS

Five patients died and three are still alive, with no evidence of disease. There are two girls and one boy in the group of living children. One of them is suffering due to second cancer (myeloblastic leukaemia). Four deaths were caused by local progression, and one patient died because of local progression accompanied by massive dissemination to the brain and spinal cord. This patient passed away before planned radiotherapy. The overall survival of all 8 patients was 5 to 73 months. The progression-free survival of all 8 patients was 3 to 73 months. All living patients received radiotherapy as part of their treatment. Two of them had total resection of the tumour and one partial. Treatment results are presented in table 1.

DISCUSSION

ATRT of the cerebral region are among tumours with the worst prognosis. Despite worldwide multiple research concerning these types of tumours, obtained treatment results are still poor. Diagnostic and therapeutic difficulties are related to the rarity of these tumours. Hence, the possibility of randomized multicentre trials assessing treatment efficiency is limited. So far, genetic and immunohistochemical research in the field of ATRT have not resulted in any significant progress in therapeutic and diagnostic procedures including differentiation between ATRT and PNET/medulloblastoma.

There are publications describing long-arm deletion of chromosome 22q and gene INI1 mutation [9, 12, 19, 20]. From the immunohistochemical point of view the following staining methods seem to be significant when differentiating ATRT from PNET: E-cadherin, N-cadherin, beta-catenin immunoreactions [21]. In Rorke's report diagnostic difficulties with distinction between ATRT and PNET/medulloblastoma did not improve treatment results. 13% of ATRT were composed purely of rhabdoid cells, 31% of ATRT had malignant mesenchymal components, 67% were PNET/ATRT [22].

Table 1. Results of treatment

Pt	Age years	Sex	Histopathology	Location	Treatment	Type of surgery	Radiotherapy	PFS months	OS months	Result
FF	4/12	M	Medulloblastoma/ATRT	Inf	S+CHT	PR	No	6	10	DOD
CD	4	F	ATRT	Sup	S+CHT	SR	No	3	5	DOD
AG	2.5	F	ATRT	Inf	S+CHT	SR	No	7	10	DOD
IM	2	F	ATRT	Sup	S+CHT+RT	PR	CSI 35Gy+boost 55Gy	73	73	NED
EN	5	F	ATRT	Sup	S+CHT+RT	TR	CSI 35Gy+boost 55Gy	72	72	NED second cancer
AG	11	M	PNET/ca.plexus chorioidei/ATRT	Sup	S+CHT+RT	TR	CSI 35Gy+boost 55Gy	7	9	DOD
WN	6	F	ATRT/PNET	Sup	S+CHT+RT+CHT	SR	CSI 35Gy+boost 55Gy	13	25	DOD
MG	22	M	ATRT	Sup	S+CHT+RT+CHT	TR	CSI 35Gy+boost 54Gy	28	28	NED

Legend:
Sup – supratentorial, Inf – infratentorial
S – surgery, CHT – chemotherapy, RT – radiotherapy
PR – partial resection, SR – subtotal resection, TR – total resection
PFS – progression-free survival
OS – overall survival
NED – no evidence of disease, DOD – dead of disease, LWD – living with disease

Numerous publications inform about misdiagnosed tumours, especially in the infratentorial location, where they resemble medulloblastoma tumours and are frequently mistaken for them [3, 5, 6, 7, 8, 11, 12]. According to the Koral report on preoperative MRI examinations of 36 patients with medulloblastoma and 19 with ATRT, conventional MRI showed similar characteristics between ATRT and medulloblastoma. Cerebellopontine angle involvement and intratumoural haemorrhage are more common in atypical teratoid rhabdoid tumour [23]. In our patients, diagnostic difficulties were noted in two cases. One patient (a boy, 4 months old) had a tumour with location and histology typical for medulloblastoma. Because of the patient's young age, only chemotherapy according to the protocol for children below 3 years old was administered. Unfortunately, disease progression was observed during chemotherapy and additionally ATRT was detected in the patient's kidney. In the case of a second child histological difficulties concerning tumour distinction between PNET, carcinoma plexus chorioidei and ATRT were noted. However, final confirmation of the ATRT diagnosis was achieved after specimen consultations and histochemical examinations (but not with immuno-histochemical data).

So far, published treatment results have not been satisfactory. Long-term survivals are very rare. Many authors have observed that older age and female gender predicted better prognosis [1, 2, 4, 13, 15, 24, 25, 26, 27]. In our study group, only one child below 3 years old and 2 older children are alive. So far no standard methods for the most effective therapy have been developed, but a review of published materials showed that high-dose chemotherapy together with radiotherapy improved survival

rate in ATRT [15]. We observed a similar effect in our study group. All living children have undergone high dose radiotherapy to the tumour bed and to the craniospinal axis as well. In St. Jude Hospital's report, concerning 31 children treated during 19 years, 2-year overall survival was 17%±8% and 89%±11% for the group of children below 3 years old and older children, respectively. There is no doubt that patient's age and the presence of radiotherapy treatment prolonged survival in the described groups of patients. In the group of younger children disease progression during chemotherapy was observed in 82% of patients and second-line chemotherapy failed. After rescue radiotherapy long-term remission was found in 2 children. There is no clear answer regarding the area of radiotherapy. However, in most cases relapses occur in the tumour bed [15]. This was also confirmed in our material; only one patient had local progression together with dissemination before planned radiotherapy.

Recently, CD133, a 5-transmembrane glycoprotein, was identified as an important marker. Chou reported that the amount of CD 133(+) in ATRT correlated positively with the degree of resistance to radiation therapy [28].

According to a multicentre register of ATRT where information about 42 children was gathered, disease-free survival longer than 2 years was achieved in 24% of patients. All living patients underwent aggressive treatment including total surgery, radiotherapy and/or intrathecal or high dose chemotherapy with stem cell graft [29]. Chen et al., in their report of 17 patients, found important prognostic factors using multivariate analysis. Those factors included: clinical status of patients, radiotherapy dose, and time between surgery and radiation therapy. Eighty percent of patients suffered from disseminated disease despite the fact that all of them received CSI. In the authors' opinion, radiotherapy is a key method of ATRT treatment. They recommend radiotherapy directly after surgical therapy [16]. Also, Mexican authors who observed 10 patients established that radiotherapy beside surgery comprised the major method of paediatric ATRT treatment [30].

CONCLUSIONS

We conclude that radiotherapy with a higher dose (i.e. over 50 Gy) prolonged survival in ATRT and should be incorporated in all treatment protocols for patients with this diagnosis. It is difficult to estimate the role of whole craniospinal axis radiotherapy because of different relapse character.

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