

# High-dose chemotherapy with autologous hematopoietic stem cell transplantation in children with atypical teratoid/rhabdoid CNS tumors

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## Summary

Atypical teratoid rhabdoid tumor (ATRT) of central nervous system (CNS) is an aggressive malignancy with poor prognosis, predominantly observed in young children. There are no established approaches to CNS ATRT management nowadays. This retrospective study aimed to analyze the effectiveness and prognostic factors of high dose chemotherapy with autologous hematopoietic stem cell transplantation HDCT/auto-HSCT in pediatric CNS ATRT. Thirty CNS ATRT patients treated with HDCT/auto-HSCT were enrolled in the analysis. Median age was 19.5 months. There were 11 (36.6%) infants and 19 (63.4%) children older than 12 months, among them 21 (70%) boys and 9 (30%) girls. Infratentorial tumor was diagnosed in 7 patients (56.7%) and supratentorial in 13 (43.3%). All children initially received surgery with total resection (n=8, 26.7%), subtotal resection (n=9, 30%), partial resection (n=11, 36.6%) and biopsy (n=2, 6.7%). The majority of patients had M+ stage (n=16, 53.3%) and the minority had M-0 stage (n=12, 40%), while stage wasn't clarified (Mx) in 2 (6.7%) cases. After surgery everyone received treatment according to

various protocols: EU-RHAB (n=12, 40%), MUV-ATRT (n=11, 36.7%), individual therapy (n=7, 23.3%). Radiotherapy (RT) was performed in 24 children (80%) after HDCT/auto-HSCT. The majority of patients (n=22, 73.3%) received intraventricular/intrathecal chemotherapy. The disease status was assessed in all cases prior to HDCT/auto-HSCT with complete response (CR) in 12 (40%), partial response (PR) in 8 (26.7%) and stabilization (S) in 10 (33.3%). Single auto-HSCT was performed in the majority of patients (n=21, 70%) and tandem transplants were carried out in 9 cases only (30%). In total, 39 transplants were performed. Peripheral blood hematopoietic stem cells (PBSC) were the transplant source in 27 children (90%), and combination of PBSC and bone marrow (BM), in 3 (10%). Five-year event-free survival (EFS) and overall survival (OS) were 44%. The majority of relapses were diagnosed during first 24 months after disease onset. These data are comparable to the most international results. Survival of CNS ATRT patients after HDCT/auto-HSCT was statistically significantly higher after total tumor resection, RT, intraventricular/intrathecal chemotherapy, and CR prior to transplantation.

## Keywords

Children, young age, atypical teratoid rhabdoid tumor, central nervous system, chemotherapy, high-dose, radiation therapy, clinical outcomes, survival, prognostic factors.

## Introduction

Central nervous system (CNS) atypical teratoid rhabdoid tumor (ATRT) is a rare aggressive malignancy, which comprises 1-2% of brain and spinal neoplasms [1, 2]. Median age at diagnosis is 1 year with male predominance 1.5:1.3 [3, 4, 5, 6]. Nowadays, there are no established standards in the treatment of CNS ATRT. Various management approaches exist for different countries and institutions. Despite this uncertainty, surgery followed by adjuvant chemotherapy and radiotherapy (in older children) is, without doubt, the cornerstone of their treatment [7, 8]. HDCT/auto-HSCT is used in children under 3 years, intending for canceling or postponing radiation therapy (RT) and reduce the risk of long-term neuro-cognitive disorders and improve outcome [9, 10, 11]. Despite intensive multimodal therapy, the majority of patients with ATRT develop relapses [10, 11, 12]. Prognosis for CNS ATRT remains dismal, especially in children with residual tumor and metastatic disease.

The aim of present study was to assess effectiveness and define prognostic factors in CNS ATRT patients after HDCT/auto-HSCT.

## Patients and methods

### Trial design

This retrospective multicentric continuous cooperative study was performed between 2008 and 2020 in V.A. Almazov NMRC, RM Gorbacheva Research Institute, Pavlov University, and Pirogov Russian National Research Medical University. Eligibility criteria: the study included 30 patients aged  $\leq 18$  with histologically verified CNS ATRT and complex treatment performed according to different protocols, including HDCT/auto-HSCT.

The surviving patients were censored by 1 February 2021. Overall survival was calculated from the date of surgery up to death or up to the last follow up. Event-free survival was calculated from the date of surgery up to the date of unfavorable event (death, relapse, progression), or up to last follow up.

### Clinical characteristics of patients

A total of 30 patients  $\leq 18$  years old with median age of 19.5 months were enrolled in the study from different regions of Russian Federation. Initial characteristics of patients are presented in Table 1. There were 11 (36.6%) infants, and 19 (63.4%) children aged over 12 months, among them 21 (70%) boys and 9 (30%) girls. Infratentorial tumor was diagnosed in 7 patients (56.7%) and supratentorial – in 13 (43.3%).

Molecular biologic subgroups were identified only in 7 patients: ATRT-SHH (n=4), ATRT-MYC (n=1) and ATRT TYR (n=2). All children initially received surgery with total tumor resection (n=8, 26.7%), subtotal resection (n=9, 30.0%), partial resection (n=11, 36.6%) and biopsy (n=2, 6.7%). The majority of patients had M+ stage (n=16, 53.3%) and minor subgroup had M-0 stage (n=12, 40%), with non-classified stage (Mx) in 2 cases (6.7%). After surgery, everyone received treatment according to various protocols: EU-RHAB (n=12, 40%), MUV-ATRT (n=11, 36.7%), individual therapy (n=7, 23.3%). There was no radiotherapy (RT) prior to HDCT/auto-HSCT in children with ATRT. RT after transplantation was performed in 24 children (80%): local RT (n=16, 60%), cranio-spinal irradiation (n=6, 20%), and no RT (n=6, 20%). The majority of patients (n=22, 73.3%) received intraventricular/intrathecal chemotherapy. Disease status was assessed in all 12 cases (40%) prior to HDCT/auto-HSCT with complete response (CR); partial response (PR), in 8 (26.7%), and stabilization (S) in 10 (33.3%). Single auto-HSCT was performed in majority of patients (n=21, 70%), and tandem transplant, only in 9 cases (30%). Total number of transplants was 39. Prior to auto-HSCT peripheral blood hematopoietic stem cells (PBSC) or bone marrow (BM) were harvested. PBSC were the transplant source in 27 children (90%), and combination of PBSC and BM was used in 3 cases (10%).

Conditioning regimen for single auto-HSCT in the majority of cases (n=13, 43.3%) consisted of thiotepa 300 mg/m<sup>2</sup>, carboplatin 500 mg/m<sup>2</sup> and etoposide 250 mg/m<sup>2</sup> on Days -6, -5, -4 (Table 2). Carboplatin 500 mg/m<sup>2</sup> and thiotepa 300 mg/m<sup>2</sup> on Days -6, -5, -4 were used in 8 patients (26.7%). First conditioning regimen consisted of carboplatin 500 mg/m<sup>2</sup> and etoposide 250 mg/m<sup>2</sup> on Days -8, -7, -6, -5 and second conditioning regimen consisted of thiotepa 300 mg/m<sup>2</sup> and cyclophosphamide 1500 mg/m<sup>2</sup> on Days -4, -3, -2 in 7 children (23.3%) with tandem transplantation. Carboplatin 510 mg/m<sup>2</sup> and thiotepa 300 mg/m<sup>2</sup> on Days -4, -3 for both transplantations were used in 2 patients (6.7%). Time interval between first and second HDCT was 4-6 weeks. Chemotherapy was calculated according to pre-transplant levels of glomerular filtration rate, cardiac output and audiometry. Mean number of infused CD34+ cells was  $4.98 \times 10^6/\text{kg}$  (1.9-9.2).

### Statistical evaluation

Data collection and clarification, systematization of initial information and visualization in digital tables were performed by means of Microsoft Office Excel (2016). Python was used for statistical analysis (Python 3.8.). Calculations were based on built-in function modules (Scipy and Lifelines).

Table 1. Characteristics of CNS ATRT patients and HDCT/auto-HSCT

Parameter	Value	
	Number	%
<b>Sex (n=30)</b>		
Male	21	70%
Female	9	30%
<b>Age at diagnosis (n=30)</b>		
<12 months	11	36.6%
>12 months	19	63.4%
Range (min-max), months	1-64	
Median, months	19.5	
<b>Tumor localization (n=30)</b>		
Infratentorial	17	56.7%
Supratentorial	13	43.3%
<b>Stage (n=30)</b>		
M0	12	40%
M+	16	53.3%
Mx	2	6.7%
<b>Tumor resection (n=30)</b>		
Total resection	8	26.7%
Subtotal resection	9	30%
Partial resection	11	36.6%
Biopsy	2	6.7%
<b>Chemotherapy protocol (n=30)</b>		
EU-RHAB	12	40%
MUV-ATRT	11	36.7%
Individual therapy	7	23.3%
<b>Radiotherapy (n=30)</b>		
Local RT	18	60%
Craniospinal irradiation	6	20%
No RT	6	20%
<b>Intraventricular/intrathecal chemotherapy (n=30)</b>		
Yes	22	73.3%
No	8	26.7%
<b>Status prior to HDCT/auto-HSCT (n=30)</b>		
Complete response	12	40%
Stabilization	10	33.3%
Partial response	8	26.7%
<b>Stem cell source (n=30)</b>		
PBSC	27	90%
PBSC+BM	3	10%

Table 2. Conditioning regimens for HDCT/auto-HSCT in CNS ATRT patients.

Drugs	Route of administration	Total dosage (mg/m <sup>2</sup> )	Number of patients (%)
<b>Single HDCT</b>			
Carboplatin	intravenous	1500	13 (43.3%)
Etoposide	intravenous	750	
Thiotepa	intravenous	900	
Carboplatin	intravenous	1500	8 (26.7%)
Thiotepa	intravenous	900	
<b>Tandem HDCT</b>			
1. HDCT			7 (23.3%)
Carboplatin	intravenous	2000	
Etoposide	intravenous	1000	
2. HDCT			
Thiotepa	intravenous	900	
Cyclophosphamide	intravenous	4500	
2 cycles of HDCT:			2 (6.7%)
Carboplatin	intravenous	1020	
Thiotepa	intravenous	600	

The Shapiro-Wilk test demonstrated absence of normal distribution of data in the study. It required usage of non-parametric statistics for further analysis.

The surviving patients were censored by 1 February 2021. Overall survival was calculated from the date of surgery up to death or last follow-up. Event-free survival was calculated from the date of intervention up to the date of unfavorable event (death, relapse, progression), or to the last follow-up. Median values describe the central values of distribution. Quantiles (Me [Q1; Q3]) and range of variation were used for assessment of variables. Mann-Whitney U-test compared independent samples in the absence of normal distribution. Nominal data obtained for independent research groups were compared using Pearson's Chi-squared test. Survival and cumulative incidence of events were calculated according to Kaplan-Meier method. Survival curves were compared using the log-rank test. Clinical outcomes were analyzed by multifactorial analysis (Cox regression). Stepwise regression was chosen for regression assessment, starting with maximal number of predictors. At each next step, the model excludes less valuable predictors. The procedure was stopped when the only independent variables remained, that were statistically significant. Statistical significance was assumed at p-value of  $\leq 0.05$ .

## Results

At the time of analysis, 18 children (60%) were alive and 12 (40%) died, among them 11 (91.6%) succumbed to ATRT progression and 1 (8.4%) to infectious complications in early post-transplant period. There were no cases of secondary tumors. Among children of ATRT-SHH molecular subgroup 2 died of progression and 2 were alive and in remission. Patient with ATRT-MYC molecular subgroup died of progression and 2 children with ATRT TYR stayed alive and in remission at the last follow up.

According to Kaplan-Meier statistical method EFS of the whole cohort (n=30) was 0.87 [0.68; 0.95] at 1 year, 0.49 [0.3; 0.67] at 2 years and 0.44 [0.24; 0.62] at 5 years (Fig. 1). Median EFS was 23 months [16.0; 102]. Worth of note, the majority of relapses in children with CNS ATRT occurred during first 24 months after diagnosis.

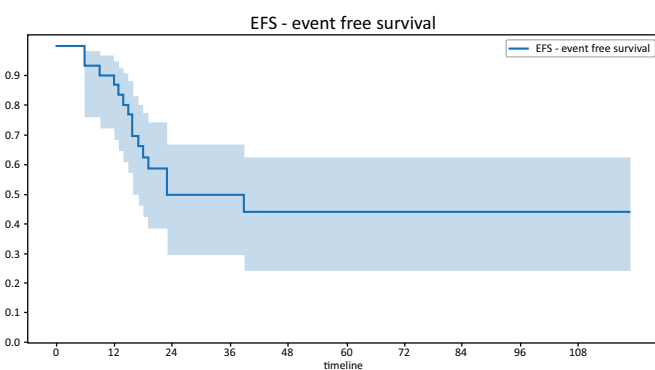


Figure 1. Event-free survival (EFS) of CNS ATRT patients after HDCT/auto-HSCT

OS was 0.97 [0.79; 1.0] at 1 year, 0.7 [0.49; 0.84] at 2 years, 0.44 [0.22; 0.64] at 5 years (Fig. 2). Median OS was 44 months [22.0; 102].

Analysis of prognostic factors in CNS ATRT patients after HDCT/auto-HSCT was performed. The results of univariate analysis are presented in Table 3.

In univariate analysis extent of resection, radiotherapy, intraventricular/intrathecal chemotherapy and disease status prior to auto-HSCT demonstrated statistically significant impact on EFS. Survival curves are presented on Figures 3a-3d.

Upon univariate analysis, EFS in patients with CNS ATRT after HDCT/auto-HSCT was statistically significantly higher after total resection compared to subtotal resection, partial resection or biopsy: 1.0 [1.0; 1.0]; 0.37 [0.07; 0.69]; 0.15 [0.01; 0.46]; 0.00 [0.00; 0.00], respectively (p<0.001) (Fig. 3A); in the patients with RT *versus* children without RT: 0.56 [0.31; 0.75] and 0.00 [0.00; 0.00], respectively (p<0.001) (Fig. 3B); in the patients with intraventricular/intrathecal chemotherapy than in children without this local approach: 0.55 [0.29; 0.75] and 0.13 [0.01; 0.42], respectively (p=0.0005) (Fig. 3C); and in complete responders prior to auto-HSCT compared to PR and stable disease: 0.88 [0.39; 0.98]; 0.0 [0.0; 0.0] and 0.47 [0.12; 0.76], respectively (p<0.001), as seen from Fig. 3D.

Such factors as extent of tumor resection, radiotherapy, intraventricular/intrathecal chemotherapy, disease status prior to HDCT demonstrated statistically significant impact on OS (the survival curves are shown on Figures 4A to 4D).

Upon univariate analysis, OS in CNS ATRT patients after HDCT/auto-HSCT was statistically significantly higher after total resection compared to subtotal resection, partial resection or biopsy: 1.0 [1.0; 1.0]; 0.62 [0.23; 0.86]; 0.0 [0.0; 0.0]; 0.00 [0.00; 0.00], 0.00 [0.00; 0.00], respectively (p<0.001), as seen in Fig. 4A; in the patients with RT compared to children without RT: 0.57 [0.29; 0.78] and 0.00 [0.00; 0.00], respectively (p<0.001) depicted in Fig. 4B; in the patients with intraventricular/intrathecal chemotherapy than in children without this local approach: 0.56 [0.25; 0.78] and 0.13 [0.01; 0.42], respectively (p=0.0001, Fig. 4C); and in complete responders prior to auto-HSCT compared to PR and stable disease: 1.0 [1.0; 1.0]; 0.0 [0.0; 0.0] and 0.0 [0.0; 0.0], respectively (p<0.001), as shown in Fig. 4D.

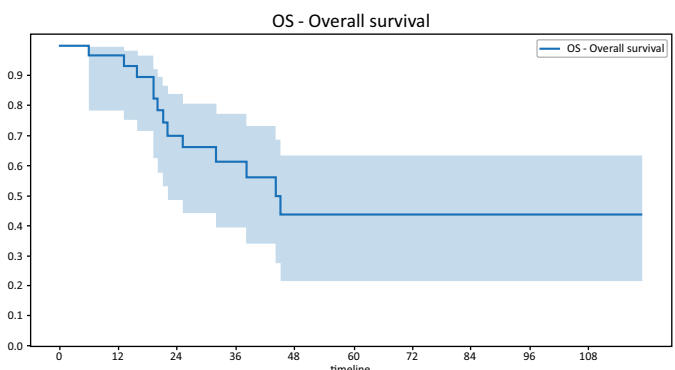
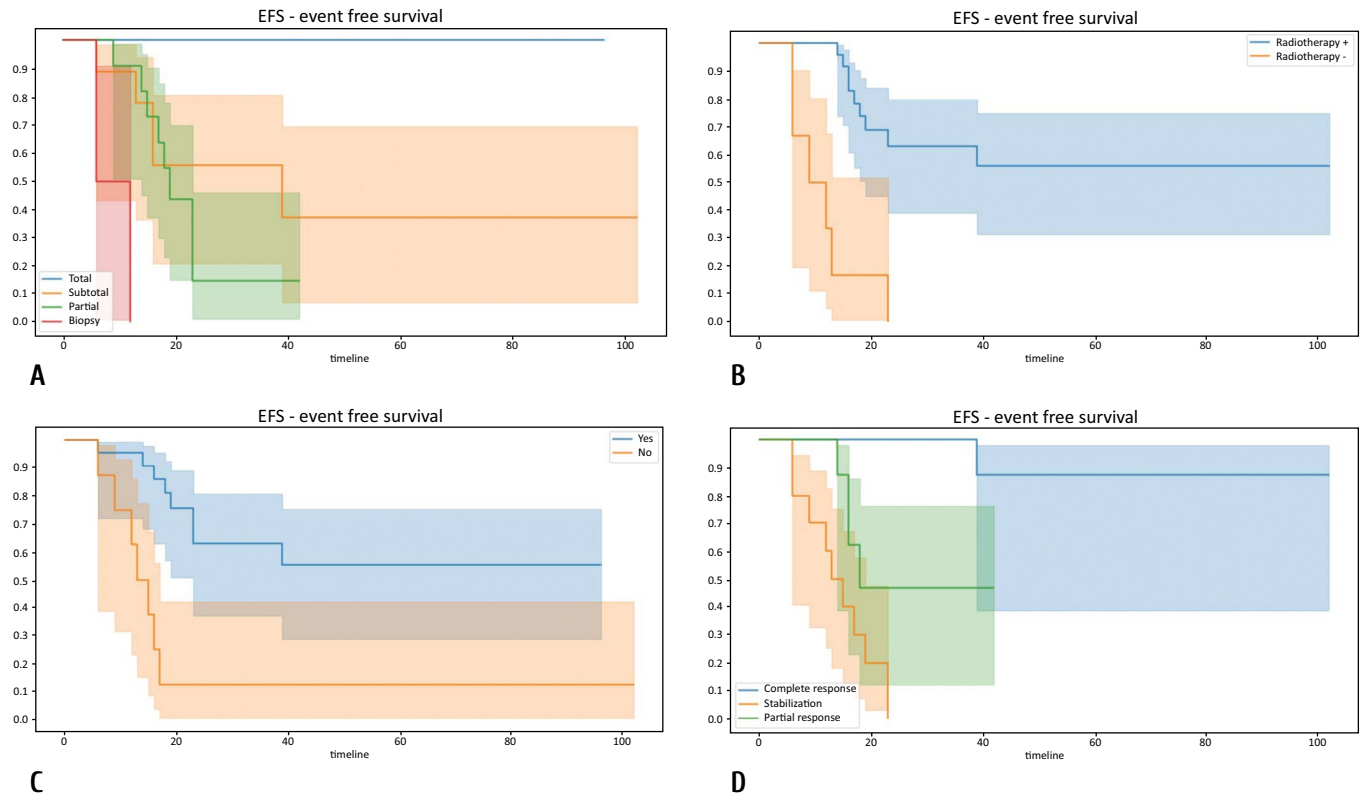


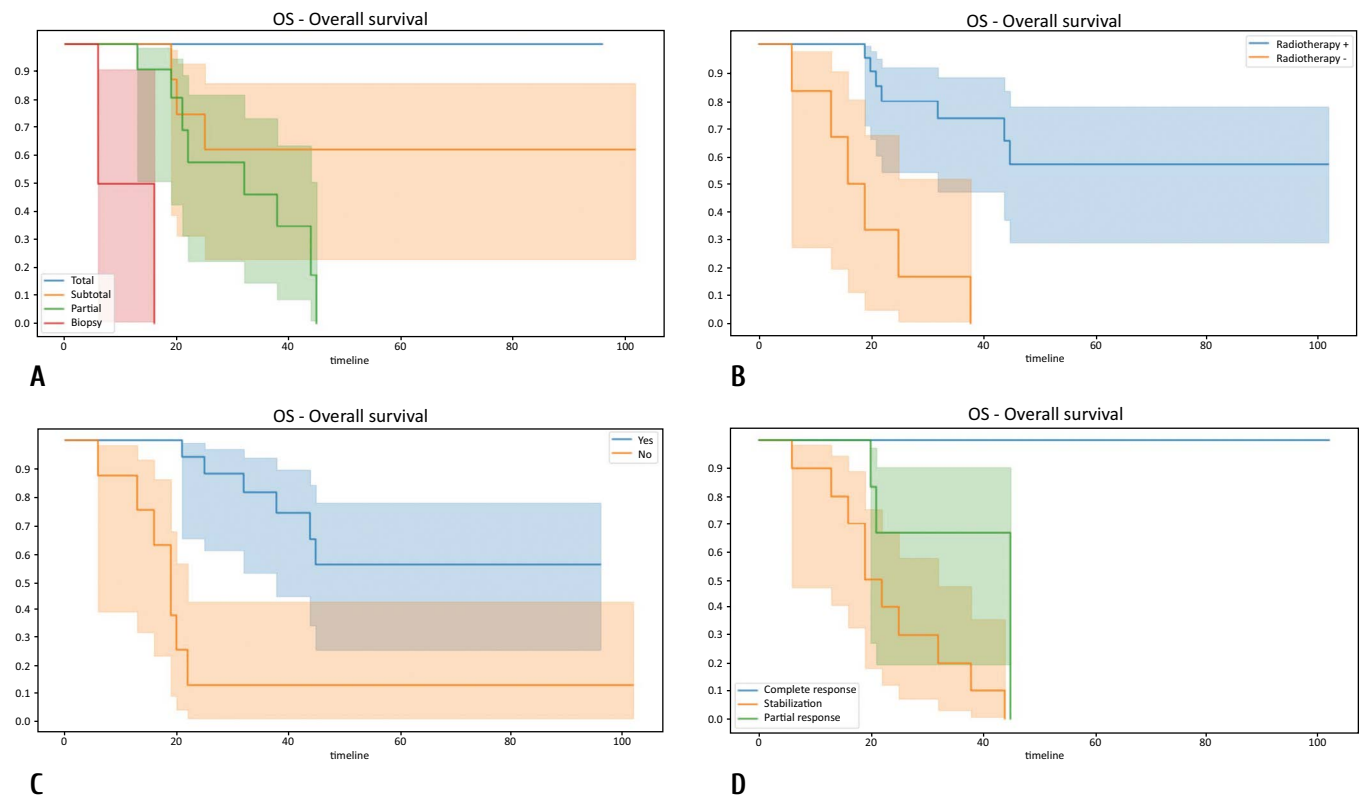
Figure 2. Overall survival in CNS ATRT patients after HDCT/auto-HSCT

Table 3. Prognosis of CNS ATRT patients after HDCT/auto-HSCT according to different factors

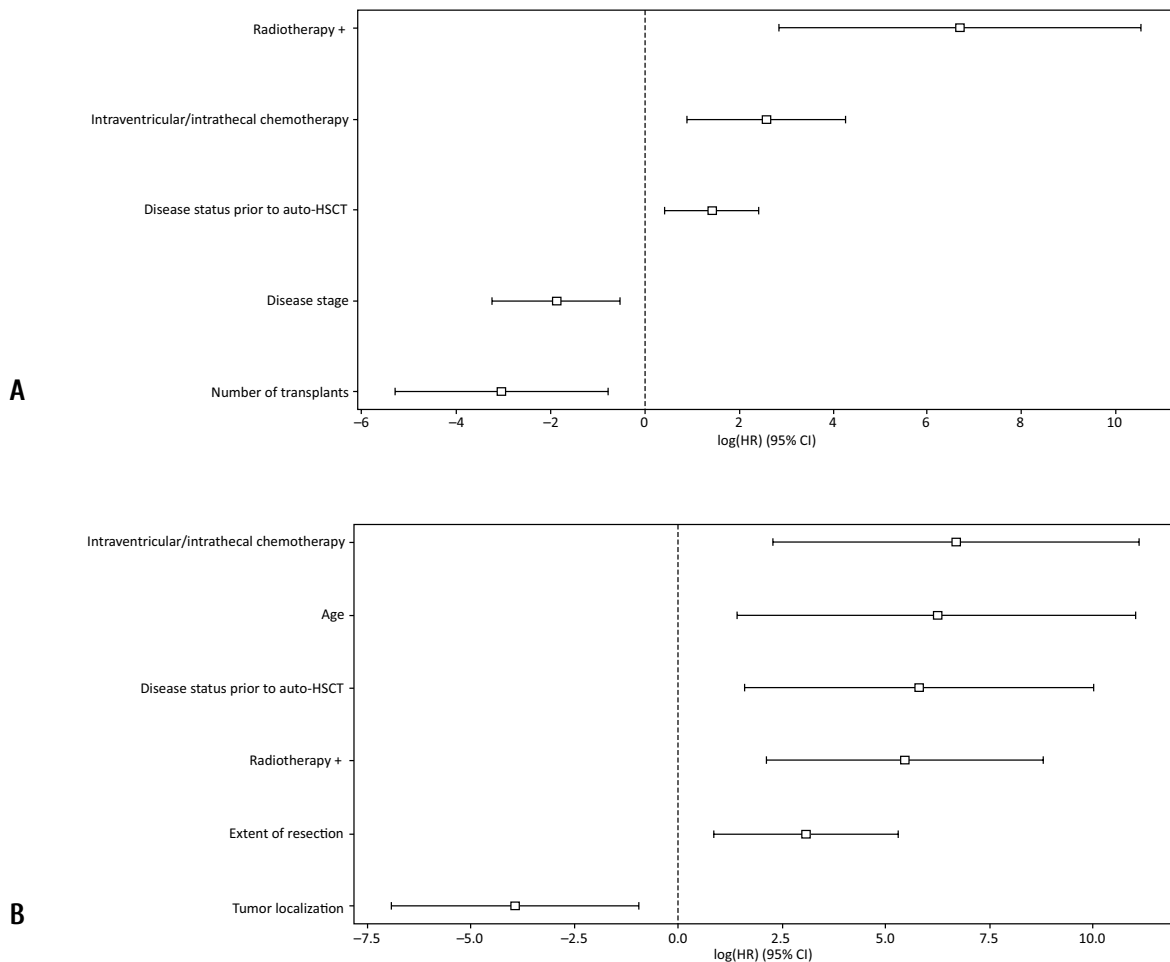
Factors	Event free survival (EFS)			Overall survival (OS)		
	Median survival [95% CI]	Median time, months [95% CI]	Log Rank, p	Median survival [95% CI]	Median time, months [95% CI]	Log Rank, p
<b>Age</b> <12 months (n=11) >12 months (n=19)	0.62 [0.28; 0.84] 0.32 [0.1; 0.57]	- [12.0; -] 23.0 [16.0; -]	0.3866	0.52 [0.15; 0.8] 0.37 [0.13; 0.62]	- [16.0; -] 38.0 [20.0; -]	0.5569
<b>Sex</b> Male (n=21) Female (n=9)	0.55 [0.31; 0.74] 0.33 [0.08; 0.62]	- [15.0; -] 23.0 [6.0; -]	0.7295	0.48 [0.2; 0.72] 0.42 [0.11; 0.71]	44.0 [19.0; -] 45.0 [20.0; -]	0.8184
<b>Tumor localization</b> Infratentorial (n=17) Supratentorial (n=13)	0.51 [0.26; 0.72] 0.23 [0.01; 0.6]	- [14.0; -] 23.0 [16.0; -]	0.6511	0.45 [0.18; 0.68] 0.4 [0.08; 0.73]	45.0 [21.0; -] 38.0 [19.0; -]	0.7290
<b>Stage</b> M0 (n=12) M+ or multifocal tumor (n=16) Mx (n=2)	0.46 [0.16; 0.72] 0.52 [0.24; 0.74] 0.0 [0.0; 0.0]	39.0 [12.0; -] - [17.0; -] 9.0 [9.0; 23.0]	0.322	0.52 [0.2; 0.77] 0.41 [0.11; 0.7] 0.0 [0.0; 0.0]	- [19.0; -] 45.0 [22.0; -] 13.0 [13.0; 38.0]	0.1952
<b>Extent of resection</b> Total (n=8) Subtotal (n=9) Partial (n=11) Biopsy (n=2)	1.0 [1.0; 1.0] 0.37 [0.07; 0.69] 0.15 [0.01; 0.46] 0.00 [0.00; 0.00]	- [-; -] 39.0 [6.0; -] 19.0 [14.0; 23.0] 6.0 [6.0; 12.0]	<0.001*	1.0 [1.0; 1.0] 0.62 [0.23; 0.86] 0.0 [0.0; 0.0] 0.0 [0.0; 0.0]	- [-; -] - [19.0; -] 32.0 [19.0; 45.0] 6.0 [6.0; 16.0]	<0.001*
<b>Chemotherapy protocol</b> EU-RHAB (n=12) MUV-ATRTR (n=11) Individual therapy (n=7)	0.4 [0.14; 0.66] 0.7 [0.33; 0.89] 0.29 [0.04; 0.61]	15.0 [9.0; -] - [16.0; -] 23.0 [6.0; -]	0.1826	0.32 [0.08; 0.6] 0.5 [0.06; 0.84] 0.43 [0.1; 0.73]	21.0 [13.0; -] 45.0 [44.0; -] 38.0 [20.0; -]	0.0854
<b>Radiotherapy</b> Radiotherapy + (n=24) Radiotherapy - (n=6)	0.56 [0.31; 0.75] 0.0 [0.0; 0.0]	- [19.0; -] 12.0 [6.0; 23.0]	<0.001*	0.57 [0.29; 0.78] 0.0 [0.0; 0.0]	- [32.0; -] 19.0 [6.0; 38.0]	<0.001*
<b>Intraventricular/intrathecal chemotherapy</b> Yes (n=22) No (n=8)	0.55 [0.29; 0.75] 0.13 [0.01; 0.42]	- [23.0; -] 15.0 [6.0; 17.0]	0.0005*	0.56 [0.25; 0.78] 0.13 [0.01; 0.42]	- [38.0; -] 19.0 [6.0; 22.0]	0.0001*
<b>Disease status prior to HDCT/auto-HSCT</b> Complete response (n=12) Stabilization (n=10) Partial response (n=8)	0.88 [0.39; 0.98] 0.0 [0.0; 0.0] 0.47 [0.12; 0.76]	- [39.0; -] 13.0 [6.0; 19.0] 18.0 [14.0; -]	<0.001*	1.0 [1.0; 1.0] 0.0 [0.0; 0.0] 0.0 [0.0; 0.0]	- [-; -] 19.0 [6.0; 32.0] 45.0 [20.0; 45.0]	<0.001*
<b>Single/Tandem auto-HSCT</b> Single (n=21) Tandem (n=9)	0.43 [0.18; 0.67] 0.44 [0.14; 0.72]	39.0 [16.0; -] 23.0 [12.0; -]	0.9284	0.39 [0.11; 0.67] 0.44 [0.14; 0.72]	45.0 [22.0; -] 38.0 [16.0; -]	0.8775
<b>Stem cell source</b> PBSC (n=27) BM+PBSC (n=3)	0.5 [0.28; 0.69] 0.0 [0.0; 0.0]	- [16.0; -] 19.0 [6.0; 23.0]	0.1006	0.53 [0.29; 0.73] 0.0 [0.0; 0.0]	- [21.0; -] 38.0 [25.0; 44.0]	0.2450



**Figure 3. Event-free survival in CNS ATRT patients after HDCT/auto-HSCT according to different factors: a – extent of resection; b – radiotherapy, c – intraventricular/intrathecal chemotherapy; d – disease status prior to auto-HSCT**



**Figure 4. Overall survival of CNS ATRT patients after HDCT/auto-HSCT according to different factors: a, extent of tumor resection; b, radiotherapy; c, intraventricular/intrathecal chemotherapy; d, disease status prior to auto-HSCT**



**Figure 5. Multivariate analysis of EFS (a) and OS (b) by Cox Proportional Hazard Model**

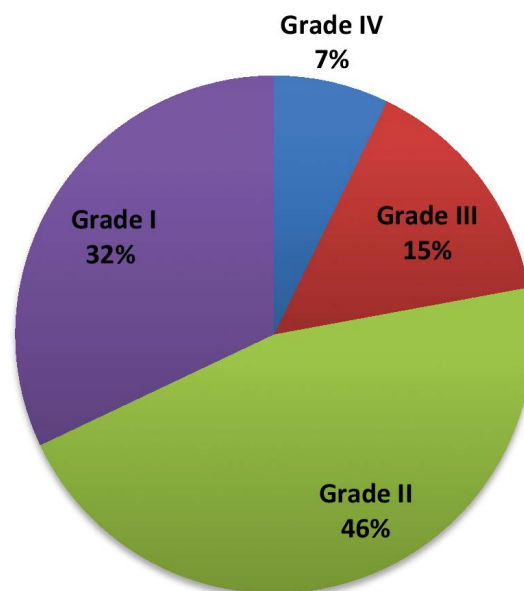
Figure 5A demonstrates that final model of EFS includes such variables as RT, disease stage, intraventricular/intrathecal chemotherapy, disease status prior to auto-HSCT, number of transplants.

Figure 5B demonstrates that final model of OS includes age, tumor localization, extent of resection, radiotherapy, intraventricular/intrathecal chemotherapy and disease status prior to auto-HSCT.

Duration of cytopenia varied from 6 to 24 days with median of 11 days after hematopoietic stem cell reinfusion. Toxicity of HDCT/auto-HSCT was assessed according to international criteria (CTCAE v.4.0), with the following items: ototoxicity, neurotoxicity, infections, nephrotoxicity, nausea/vomiting, mucositis, skin toxicity, hepatotoxicity, lung toxicity, cardiotoxicity.

During the study period, 21 single and 9 tandem transplants were performed in 30 patients. Total number of transplants reached 39, and they were separately analyzed according to 5-scale CTCAE recommendations. Distribution according to toxicity was as follows: Grade I – 32% (n=58), Grade II – 46% (n=83), Grade III – 15% (n=27) and Grade IV – 7% (n=13) as shown in Fig. 6.

Fig. 7 demonstrates that that the majority of Stage IV complications were mucositis and infections (sepsis).



**Figure 6. Toxicity distribution according to CTCAE in CNS ATRT patients after HDCT/auto-HSCT**





conditioning regimens for tandem and single auto-HSCT were used. OS and EFS at 2 years were 50% and 29%, respectively. There was no TRM [16]. In our study 12 patients treated according to EU-RHAB demonstrated OS and EFS of 40% and 32%, respectively.

Fossey and coauthors showed improved 5-year OS in ATRT patients under 1 year of age after HDCT/auto-HSCT compared to infants without HDCT (52.0% vs 10.7% respectively,  $p < 0.001$ ). Patients with CR prior to HDCT had significantly higher OS [17]. It underlines the importance of disease status prior to HDCT for prognosis and it is necessary to thoroughly select patients for HDCT.

It is worth of discussing the results obtained by Medical University of Vienna in CNS ATRT patients with M0-M3 stage (MUV). Treatment in post-surgery period included 3 blocks of 9-week chemotherapy with anthracyclines, alkylating agents, HD-MTX with addition of intrathecal chemotherapy (etoposide and cytarabine) and subsequent HDCT/auto-HSCT. Local RT was postponed until the end of chemotherapy. This cohort of patients demonstrated 100% OS and  $88.9 \pm 10.58\%$  EFS at 5 years, thus being significantly higher as for the control group (OS =  $56.3 \pm 11.3\%$ ; EFS =  $52.9 \pm 11\%$ ) treated with various other approaches. According to data of these workers, chemotherapy was well tolerated, timing delays and dose reduction due to toxicity were minimal [18]. In our study, 11 patients treated according to MUV protocol showed 3-year OS and EFS of 70% and 50%, respectively. These results are higher than in patients treated by other protocols, however, without significant difference.

In a recent study by Yamasaky et al. [19], in a group of 34 CNS ATRT patients, 19 received HDCT/auto-HSCT with tandem ( $n=13$ ) transplantations in the majority of cases. Conditioning regimen consisted of thiotepa and melphalan. Two patients succumbed to sepsis in early post-transplant period. The study demonstrated better OS ( $p=0.025$ ) in CNS ATRT patients after HDCT/auto-HSCT compared to patients without HDCT. Protocol ACNS 0333 for the treatment of ATRT has been recently developed by the Children's Oncology Group (COG). It consists of induction chemotherapy combined with 3 cycles of HDCT/auto-HSCT and RT. The abovementioned study ( $n=65$ ) demonstrated 4-year EFS and OS of 48% and 57%, respectively [9].

## Conclusion

HDCT/auto-HSCT is an important treatment option for children with chemosensitive CNS ATRT. In our study, 5-year EFS and OS rates after transplantation were 44%. The majority of relapses occurred during 24 months after diagnosis. These results are comparable to the majority of international studies. Survival of CNS ATRT patients after HDCT/auto-HSCT was significantly higher after total tumor resection, radiotherapy, intraventricular/intrathecal chemotherapy and complete response prior to auto-HSCT. Thus HDCT/auto-HSCT can postpone RT in younger children with CNS ATRT, but cannot substitute it. There was no statistical significant difference in survival between the patients following single and tandem transplantations. According to our data, HDCT/auto-HSCT demonstrated acceptable

toxicity. Low incidence of CNS ATRT in children requires a large-scale multicentre randomized trials aiming for stratifying the patients into risk groups on the basis of clinical data, and clear indications for HDCT/auto-HSCT are crucial.

## Conflict of interest

None reported.

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# Высокодозная полихимиотерапия с аутологичной трансплантацией гемопоэтических стволовых клеток у детей с атипичной тератоид-рабдоидной опухолью центральной нервной системы

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## Резюме

Атипичная тератоид-рабдоидная опухоль (АТРО) центральной нервной системы (ЦНС) – это агрессивная злокачественная опухоль, встречается преимущественно у детей младшего возраста и характеризуется плохим прогнозом. В настоящее время нет единых стандартов лечения АТРО ЦНС. Данное ретроспективное исследование выполнено с целью оценки результатов высокодозной полихимиотерапии (ВДХТ) с последующей аутологичной трансплантацией гемопоэтических стволовых клеток (ауто-ТГСК) у детей с АТРО ЦНС и определения влияния различных факторов прогноза на выживаемость. В исследование включены 30 больных с АТРО ЦНС, которые в протоколе терапии получали ВДХТ с ауто-ТГСК. Медиана возраста пациентов составила 19,5 месяцев [9; 27]. Распределение пациентов в зависимости от возраста было следующим: младше 12 месяцев – 11 (36,6%), старше 12 месяцев – 19 (63,4%); по полу: мальчиков – 21 (70%) и девочек – 9 (30%). Опухоль у 17 пациентов (56,7%) локализовалась инфратенториально, у 13 (43,3%) – супратенториально. Всем пациентам инициально выполнено хирургическое лечение в различных объемах: тотальное удаление опухоли – у 8 (26,7%) пациентов, субтотальное – у 9 (30,0%), частичное удаление – у 11 (36,6%), биопсия – у 2 (6,7%). В анализируемой группе преобладали больные с М+ стадией заболевания – 16 пациентов (53,3%), у 12 (40,0%) метастазирование и опухолевые клетки отсутствовали, установлена М0-стадия, у 2 (6,7%) – стадия заболевания не уточнена (Мх). Все пациенты после удаления опухоли получали лечение по различным протоколам терапии: 12 пациентов (40,0%) – по протоколу

EU-RHAB, 11 (36,7%) – по протоколу MUV-ATRT, у 7 (23,3%) больных выполняли индивидуальные схемы. ЛТ проведена 24 больным (80%) после ВДХТ с ауто-ТГСК. Интратекальное/интравентрикулярное введение химиопрепаратов получили большинство пациентов (n=22, 73,3%). Статус заболевания оценивался у всех пациентов до выполнения ВДХТ с ауто-ТГСК: полный ответ (ПО) был зарегистрирован у 12 пациентов (40%), стабилизация болезни (СБ) – у 10 (33,3%), частичный ответ (ЧО) – у 8 (26,7%). Большинству пациентов выполнена однократная ауто-ТГСК – 21 (70%), тандемная ауто-ТГСК – у 9 (30%) пациентов. Общее количество выполненных ауто-ТГСК у пациентов с АТРО ЦНС составило 39. В качестве источника трансплантата в 90% (n=27) были использованы СКПК, у 10% (n=3) больных использовали комбинацию СКПК+КМ. Результаты: 5-летняя БСВ и ОВ составили 44%, большинство рецидивов диагностировано в течение 24 месяцев после постановки диагноза. Эти результаты сопоставимы с большинством международных данных. Выживаемость пациентов с АТРО ЦНС, получивших ВДХТ с ауто-ТГСК, статистически достоверно выше была при выполнении тотальной резекции опухоли, проведении ЛТ и регионарной химиотерапии и достижении ПО к моменту проведения ТГСК.

## Ключевые слова

Дети, младший возраст, атипичная тератоид-рабдоидная опухоль, центральная нервная система, химиотерапия, высокодозная, лучевая терапия, результаты лечения, выживаемость, прогностические факторы.