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ORIGINAL ARTICLE

Adjuvant chemotherapy after reduced craniospinal irradiation dose in children with average-risk medulloblastoma: A 5-year follow-up study

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Summary

Purpose: *This study was undertaken to determine the effect of adjuvant chemotherapy combined with reduced-dose craniospinal irradiation (CSI) on survival and neurocognitive sequelae of radiotherapy (RT) in patients with average-risk medulloblastoma above the age of 3 years.*

Methods: *Thirty-three children between 3 and 10 years of age with average-risk medulloblastoma were treated with postoperative reduced-dose CSI (24.0 Gy) and 30.6 Gy of local RT (total of 54.6 Gy) and then with adjuvant chemotherapy consisting of cisplatin, vincristine, and cyclophosphamide every 4 weeks for 8 cycles.*

Results: *At 5 years, event-free survival (EFS) was 79%, while overall survival (OS) was 85%. Sites of relapse were local in 3%, neuraxis in 9% and both local and neuraxis in 9% of the patients. Chemotherapy was well tolerated. Hematopoietic toxicity was the most predominant side effect followed by vomiting and ototoxicity. No grade III or IV nephrotoxicity or neurotoxicity and no treatment-related deaths were encountered. Insignificant decline of intelligence quotient (IQ) was reported in 28.6% of the patients.*

Conclusion: *The preliminary results of adjuvant chemotherapy after reduced-dose CSI in average-risk medulloblastoma patients are encouraging and effective, and can be applied safely with acceptable toxicity.*

Key words: *chemotherapy, childhood medulloblastoma, irradiation, neurocognition, survival*

Introduction

Medulloblastoma represents 20% of pediatric central nervous system (CNS) tumors and 40% of all posterior fossa tumors [1]. Although surgery and craniospinal irradiation have been the mainstay of treatment, OS rates of less than 50-60% have encouraged the use of adjuvant chemotherapy. The impact of chemotherapy in improving survival has been documented largely in patients with advanced disease at diagnosis [2]. Studies have demonstrated the adverse neurocognitive sequelae associated with RT in children with brain tumors, reporting significant declines in IQ over time among patients treated with cranial irradiation [3-6]. Strategies for dose reduction of CSI and delay of RT or avoiding RT by administering postoperative chemotherapy have been investigated and have shown evidence of improved survival rates [7,8].

Reducing the dose to neuraxis in the absence of chemotherapy has produced limited success [9]. Several approaches have been taken to reduce the side effects of RT including reduction of the neuraxis dose to 18 Gy [10], supplementing lower dose CSI with radiolabeled antibodies [11], intensified systemic chemotherapy and high dose marrow ablative chemotherapy with or without RT [12,13].

Hyperfractionated RT is another approach to reduce treatment-related toxicity; the underlying principle is that smaller doses administered twice a day reduce long term effects [14]. Hyperfractionation appears to be equally effective as once-a-day treatment, provided the total dose is slightly increased. Kortmann et al. [15] concluded that

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upfront RT with maintenance chemotherapy is more effective and neoadjuvant chemotherapy caused higher RT myelotoxicity and more RT interruptions.

Based on these data, we conducted this prospective study aiming at evaluating the effect of adjuvant chemotherapy combined with reduced dose of CSI on survival and neurocognitive sequelae of RT in patients with average-risk medulloblastoma aged 3 years and above.

Methods

From January 2005 through December 2008, 33 patients with newly diagnosed average-risk medulloblastoma aged between 3 and 10 years were enrolled onto this prospective study. All patients had contrast-enhanced magnetic resonance imaging (MRI) brain studies preoperatively and postoperatively. All of the patients underwent tumor resection prior to RT; gross-total resection (GTR) was recorded when patients had no evidence of disease on postoperative neuroimaging. Near-total resection (NTR) was defined when >90% tumor resection was visible on post-operative neuroimaging. Average-risk medulloblastoma was defined as no residual tumor or residual tumor < 1.5 cm^2, Chang stage T1-T3b, no evidence of dissemination by MRI of the brain and spine or celebrospinal fluid (CSF) cytology. Other eligibility criteria were: ECOG performance status (PS) of 0-2 and no prior RT or chemotherapy.

Detailed medical history was taken from all patients who were subjected to clinical examination including neurocognitive evaluation. Laboratory investigations included: complete blood count (CBC), electrolytes, blood urea, creatinine clearance and liver function tests. Baseline audiogram, bone scan and bone marrow aspiration (if clinically indicated e.g. abnormal CBC or bone pain) were obtained before study entry to exclude extraneural metastases. Informed consent was obtained from all patients' parents or legal guardians.

Radiation therapy

CSI was started within 28 days of resection at a dose of 24 Gy, followed by posterior fossa irradiation of 30.6 Gy (total 54.6 Gy). The cranial portion was treated by parallel-opposed lateral fields while the spinal portion was treated through single direct or 2 direct-gaped fields to the level of S2 vertebra. The spinal fields were appropriately matched, the match lines were shifted every 10 Gy to avoid overdosing or underdosing to segments of the spinal cord (1.5 Gy/fraction/day, 5 days/week). The posterior fossa was irradiated through 2D conformal technique and the planning target volume (PTV) included the entire posterior fossa volume with additional margin of 0.5 cm to account for uncertainty in immobilization and daily patient positioning. RT was given at rate of 1.8 Gy/fraction/day, 5 days per week.

Chemotherapy

Chemotherapy was initiated 6 weeks after the end of RT, and consisted of cisplatin 75 mg/m^2 i.v. infusion over 6 h on day 1 with hydration and diuresis; vincristine 1.5 mg/m^2 i.v. weekly (days 1,8,15,22); and cyclophosphamide 1000 mg/m^2 i.v. over 60 min on days 21 and 22. Chemotherapy cycles were repeated every 28 days up to a total of 8 cycles. Laboratory investigations and audiogram were done before each cycle. In case of ≥ grade 3 neurotoxicity, the dose of vincristine was reduced by 25% in the subsequent cycles. In case of ≥ grade 3 thrombocytopenia or neutropenia, the cycle of chemotherapy was delayed until fall of toxicity to grade 0-1. Cisplatin was not administered if creatinine clearance was <50% of baseline value and if it was <75% of baseline value, cisplatin was reduced by 50%.

Treatment toxicity was evaluated according to the National Cancer Institute- Common Toxicity Criteria (NCI-CTC) (version 3.0) [16].

Neurocognitive evaluation

Neurocognitive testing was evaluated twice; firstly after surgery and before the start of RT and secondly at the end of the study 5 years after diagnosis (only 28 patients were included as 5 patients had died 5 years after the diagnosis). Age-appropriate Wechsler scale of intelligence [17] was used to estimate IQ. These tests, regardless of version, result in age-corrected scores with a mean of 100 and a standard deviation of 15. Severe mental retardation was considered if IQ score was <70.

Patients were monitored regularly after completion of therapy. Neuroimaging and clinical assessments were performed every 3 months for the first year and every 6 months for 3 years after treatment and annually thereafter. End points were OS and EFS, and neurocognitive sequelae of RT.

Statistics

Distributions of survival functions were estimated using the Kaplan-Meier method. Non-normally distributed data was expressed as number and percentage, while normally distributed was expressed as mean and standard deviation. Paired sample t-test was used to compare means. P values of <0.05 were considered significant. OS was measured from the date of diagnosis to death or date of last follow

Results

Twenty-one boys and 12 girls aged 3-10 years (median 5.5) were studied and Table 1 shows their characteristics. Gross total resection was achieved in 81.8% of the patients, T1 and T2 tumors were more common, and 54.5% of the patients had ECOG PS 0.

During RT, acute toxicity was mild and toler-

Table 1. Patient characteristics

Characteristics	*Patients N (%)*
Age, years, median (range)	5.5 (3-10)
Sex	
Male	21 (63.6)
Female	12 (36.4)
Extent of surgery	
Gross total resection	27 (81.8)
Near total resection	6 (18.2)
T stage	
T_1	12 (36.4)
T_2	11 (33.3)
T_{3a}	7 (21.2)
T_{3b}	3 (9.1)
ECOG PS	
0	18 (54.5)
1	13 (39.4)
2	2 (6.1)

able with no interruption of RT sessions. Toxicity due to chemotherapy was easily manageable with no grade 4 toxicity encountered. Cycles were delayed in 3 patients (9%) because of grade 3 neutropenia and thrombocytopenia. Myelosuppression was the predominant toxicity followed by vomiting (grade 3 in 6%) and ototoxicity (grade 3 in 3%) as shown in Table 2. No treatment-related deaths occurred.

After a median follow-up of 48 months (range 14-54) local relapse in the posterior fossa was observed in 3% of the patients, distant relapse (neuraxis) in 9%, and both local and neuraxis in 9% (Table 3). No extraneural relapse was detected. Five-year OS rate was 85% (Figure 1), while EFS was 79% (Figure 2).

Cross-sectional IQ analysis

The incidence of severe mental retardation (MR) (i.e. IQ <70) was evaluated in 28 surviving patients 5 years after diagnosis/treatment. Only 5 (17.9%) patients showed severe MR before the start of RT, compared to 8 patients (28.6%) at the end of the study.

Neurocognitive evaluation revealed insignificant decline in the mean IQ values after RT compared to values before it (Table 4).

Discussion

The side effects attributed to RT have been a primary concern in the design of clinical trials for medulloblastoma during the past two decades. The concern has been greatest for patients with average-risk medulloblastoma as they have long-term disease control and the side effects have lasting impact. The severity of sequelae, especially intellectual loss, has led to attempts to reduce the dose of CSI in children with non disseminated disease.

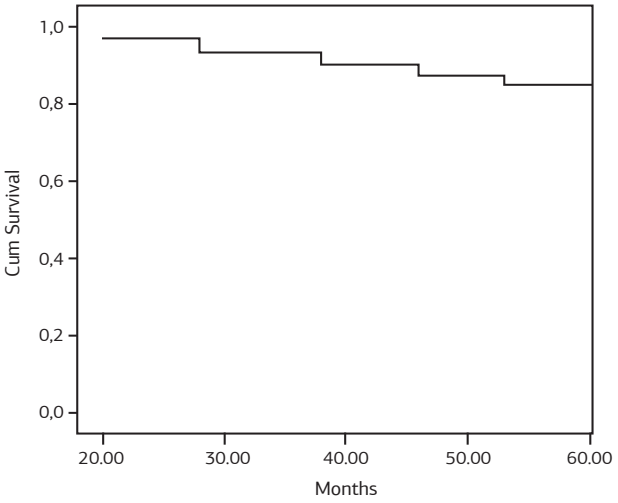

Figure 1. Overall survival.

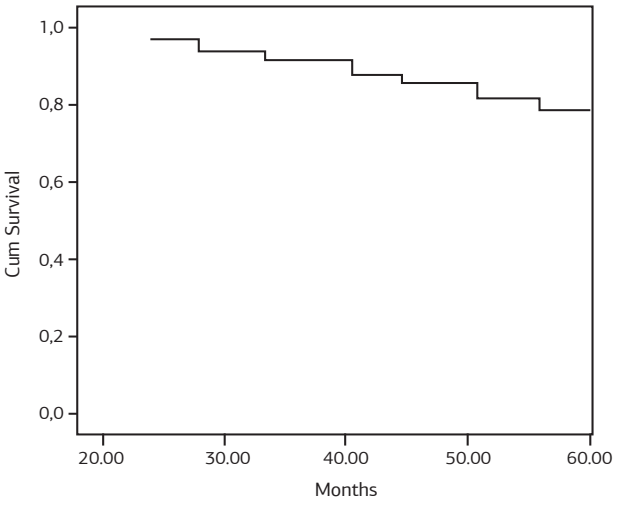

Figure 2. Event free survival.

Hematologic suppression associated with postoperative chemotherapy may delay the initiation of RT and may cause difficulties in completing CSI [18]. The chemotherapeutic approach used in this study was well tolerated. Hematopoietic toxicity was the predominant side effect of our regimen, comparable to that reported by Abd-El-Aal et al. [19].

In a study [15] ototoxicity of cisplatin was reported to be 7%, and 34% in another one [19], compared to 27% in the present study. No grade III or IV nephrotoxicity or neurotoxicity were encountered in our patients, similar to the findings of El-Sawy [20].

The sites of failure in the present series cause concern. Posterior fossa relapse (3%) was less com-

Table 2. Toxicity of chemotherapy

Toxicity	*Grade*							
	1		*2*		*3*		*4*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Vomiting	5	15	3	9	2	6	0	0
Neutropenia	7	21	3	9	3	9	0	0
Thrombocytopenia	8	24	4	12	2	6	0	0
Anemia	7	21	5	15	3	9	0	0
Ototoxicity	6	18	2	6	1	3	0	0
Nephrotoxicity	1	3	2	6	0	0	0	0
Neuropathy	4	12	2	6	0	0	0	0

mon than neuraxis alone (9%) or both posterior fossa and neuraxis (9%). In a study which utilized 36 Gy of CSI, isolated posterior fossa relapse was less common as well [21]. Possibly a subset of initially non disseminated medulloblastomas are likely to relapse outside the primary tumor site, depending on the CSI dose and due to a not fully defined biologic predisposition [22].

Our results demonstrate that children with average-risk medulloblastoma older than 3 years can be treated with considerable efficacy by adjuvant chemotherapy after reduced-dose CSI. In the present study OS and EFS rates (85 and 79%, respectively) were higher than the ones reported in some studies that used 36 Gy or more alone [23-25], but similar to that reported by Packer et al. who used reduced CSI dose [26]. As patients in this study received chemotherapy after RT, no direct conclusions can be drawn concerning the relative merits of pre- vs -post RT chemotherapy. However, a French Society of Pediateric Oncology study, treating a cohort of patients similar to ours with preirradiation chemotherapy and 25 Gy of CSI after surgery, found a 5-year EFS rate of approximately 65%, which seems inferior to our results [27].

Patients with medulloblastoma are known to develop a variety of cognitive deficits that are associated with specific functional subunits of the brain [28].

Table 3. Pattern of relapse

Site	*Patients*	
	N	*%*
Local (PF)	1	3
Distant (neuraxis)	3	9
Both local and distant	3	9

PF: posterior fossa

These deficits are secondary to a variety of factors such as age at the time of treatment, sex, hydrocephalus, RT dose and the volume of brain that received RT [29]. Severe decline of IQ was found in 28.6% of the patients, comparable to that reported by Spiegler et al. [6] and less than the one observed by Abd El-Aal et al. [19]. Also, Mulhern et al. [29] found that patients who received cranial doses ≥ 33Gy had greater IQ decline than those receiving ≤ 24Gy.

The next generation trials are underway to test the ability of proton beam RT to limit the cognitive decline in these patients.

Conclusion

The preliminary results of adjuvant chemotherapy after reduced-dose of CSI in patients with average-risk medulloblastoma are encouraging, seem to be effective and can be applied safely with acceptable toxicity.

Table 4. Neurocognitive evaluation (N=28)

	Before RT	*After RT*	*95% CI*	*p-value*
Intelligence quotient (mean±SD)	91.11±19.43	87.64±22.02	-4.9781 to 7.42639	0.07

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