Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03564-y

CLINICAL STUDY

Reduced-dose craniospinal irradiation is feasible for standard-risk adult medulloblastoma patients

Maura Massimino[1] · Marie Pierre Sunyach[2] · Francesco Barretta[3] · Lorenza Gandola[4] · Anna Garegnani[5] · Emilia Pecori[4] · Filippo Spreafico[1] · Alice Bonneville-Levard[6] · David Meyronet[7] · Carmine Mottolese[8] · Luna Boschetti[1] · Veronica Biassoni[1] · Elisabetta Schiavello[1] · Carlo Giussani[9] · Giorgio Carrabba[10] · Barbara Diletto[4] · Federica Pallotti[11] · Roberto Stefini[12] · Andrea Ferrari[1] · Monica Terenziani[1] · Michela Casanova[1] · Roberto Luksch[1] · Cristina Meazza[1] · Marta Podda[1] · Stefano Chiaravalli[1] · Nadia Puma[1] · Luca Bergamaschi[1] · Carlo Morosi[16] · Giuseppina Calareso[16] · Felice Giangaspero[13,14] · Manila Antonelli[13] · Francesca Romana Buttarelli[15] · Didier Frappaz[6]

Received: 21 April 2020 / Accepted: 16 June 2020

Abstract

Introduction Medulloblastoma is the most common malignant brain tumor in children, but accounts for only 1% of brain cancers in adults. For standard-risk pediatric medulloblastoma, current therapy includes craniospinal irradiation (CSI) at reduced doses (23.4 Gy) associated with chemotherapy. Whereas most same-stage adult patients are still given CSI at 36 Gy, with or without chemotherapy, we report here on our use of reduced-dose CSI associated with chemotherapy for older patients.

Methods We gathered non-metastatic patients over 18 years old (median age 28 years, range 18–48) with minimal or no residual disease after surgery, no negative histological subtypes, treated between 1996–2018 at the Centre Léon Bérard (Lyon) and the INT (Milano). A series of 54 children with similar tumors treated in Milano was used for comparison.

Results Forty-four adults were considered (median follow-up 101 months): 36 had 23.4 Gy of CSI, and 8 had 30.6 Gy, plus a boost to the posterior fossa/tumor bed; 43 had chemotherapy as all 54 children, who had a median 83-month follow-up. The PFS and OS were 82.2 ± 6.1% and 89 ± 5.2% at 5 years, and 78.5 ± 6.9% and 75.2 ± 7.8% at ten, not significantly different from those of the children. CSI doses higher than 23.4 Gy did not influence PFS. Female adult patients tended to have a better outcome than males.

Conclusion The results obtained in our combined series are comparable with, or even better than those obtained after high CSI doses, underscoring the need to reconsider this treatment in adults.

Keywords Adult medulloblastoma · Craniospinal irradiation · Chemotherapy · Side-effects

Introduction

While medulloblastoma (MB) is the most common malignant brain tumor in children (annual incidence: 6.5 cases/million), it is very rare in adults, accounting for less than 1% of all intracranial tumors (annual incidence: 0.6/million) [1–3]. The median age of adults diagnosed with MB is around 30 years [4].

MB in adults differs biologically from its pediatric counterpart [5, 6]. At least one in two cases of adult MB (50–60%) belong to the SHH subgroup, most often located in the cerebellar hemispheres. They mainly involve mutations implicating a loss of function in PTCH1, with some TP53 mutations, which may be somatic or germline. The prognosis is intermediate, with a 5-year OS of 70% for patients without p53 mutation [6].

As prospective studies on adults are scarce, MB is largely managed on the strength of pediatric trials. Large retrospective studies have also been instrumental in providing the rationale for treatment recommendations [4, 7]. Since adults are perceived as tolerating radiotherapy better than children (though this issue has been poorly studied), and chemotherapy less well, only adults with high-risk disease were generally given chemotherapy. This approach has

✉ Maura Massimino
maura.massimino@istitutotumori.mi.it

Extended author information available on the last page of the article

Published online: 21 June 2020

recently changed somewhat, albeit with a marked variability in the type of chemotherapy administered. The majority of adults have continued to receive 36 Gy of CSI, however, although—in the long run—the toxicity of high supratentorial doses becomes more pronounced [8]. To shed more light on the possibility of using very similar treatments for adults as for homogeneously-staged children with similar prognostic parameters, we retrospectively gathered and analyzed all MB patients over 18 years of age without metastases, with minimal or no residual disease after surgery who had been given reduced doses of CSI associated with chemotherapy between April 1996 and 2018 at the Centre Léon Bérard (CLB, Lyon, France) and the INT (Milano, Italy). We compared this sample with a similar,contemporary series of children treated in Milano between 2006 and 2018. Acute and late effects of treatments were also compared when available in patients' clinical records.

Patients and methods

The inclusion criteria for our retrospective analysis were:

1. Consecutive patients with newly-diagnosed MB with no metastases, residual disease after surgery less than 1.5 cm^2 as largest diameter on an axial view;
2. No large-cell/anaplastic histotype;
3. No prognostically negative histological/biological factors (when pertinent diagnostics were available);
4. No history of other cancers;
5. age $\geq$ 18 years for adults, and $<$ 18 years for children;
6. CSI dose not exceeding 30.6 Gy on neuraxis;
7. Treatment delivered in the two recruiting centers

All patients were staged using whole central nervous system MRI before or after surgery, and brain MRI as soon as possible after surgery. Imaging was centrally reviewed in treating centers.

Adult patients at the CLB were treated differently over time. In the latter part of the 1990s and up until 2003 they mostly received a total CSI dose of 30.6 Gy plus a boost to the posterior fossa (PF) or tumor bed (TB) up to a total dose of 54 Gy, administered in daily doses of 1.8 Gy. CSI was usually preceded or followed by chemotherapy, mainly according to the "eight-in-one" schedule [9]. From 2003 onwards, all patients received instead CSI for a total dose of 23.4 Gy. All these latter patients also received chemotherapy, which usually involved a double course of carboplatin (160 mg/m^2/day for five days) and etoposide (100 mg/m^2/day for 5 days) before and/or after irradiation [10].

Adults and children with MB treated at the INT in Milano from 2006 to 2018 all received the same treatment, based on the standard approach deriving from the results obtained with the PNET-4 protocol [11] for children. CSI was delivered at a total dose of 23.4 Gy, with a boost to the PF or TD, reaching 54 Gy altogether, with daily fractions of 1.8 Gy. Adjuvant chemotherapy after radiotherapy (RT) consisted of 8 courses of lomustine, vincristine and cisplatin or carboplatin, following the same stopping rules as for the published protocol [11]. No vincristine was administered during irradiation in any of the patients.

All patients and parents (for the children's group) gave their consent to treatment.

Acute toxicity data were available from their clinical records and are reported here for the patients treated in Milano. All patients were routinely followed up for tumor recurrence and late effects, which are also reported for adults, where available.

Survival analyses were performed used the Kaplan–Meier method. Statistical differences in overall survival (OS) and progression-free survival (PFS) were tested with the log-rank test, and all "p" values were two-tailed. The mean values of these variables are given with their 95% confidence intervals. Fisher's test was used to compare the frequency of patients' characteristics. PFS rates were estimated from the day of the first tumor excision to the time of progression, or the date of the latest follow-up visit for patients remaining in first complete remission. OS rates were estimated from the day of the first tumor excision up until death, or the date of the latest follow-up visit for patients who were still alive.

The IRB in Milano approved this observational protocol and the data protection structure as INT 100/19.

Results

At the time of writing, the median follow-up was 101 months (range 20–227) for the adult patients, and 83 months for the children (range 18–161), and all patients were off treatment.

Patients' features

There were 44 adults with a median age at diagnosis of 28 years (range 18–48); 24 of them were males. The group of children included 54 patients with a median age at diagnosis of 9.5 years (range 4–17) and 28 were boys.

Data on residual disease (always less than 1.5 cm^2 in size) showed only one adult with residual tumor (a proportion comparable with the 2/54 children showing measurable disease); none of the patients revealed metastases. Cerebrospinal fluid (CSF) cytology was conducted for all patients after surgery, revealing no metastases in the CSF compartment. The primary tumor site was vermian in 24/44 adults and 50/54 children, while it was lateral in the cerebellar hemispheres in 20 adults and 4 children, respectively ($P < 0.0001$). After centralized review, the

histological subtype for adults was classic in 14/44 cases, nodular/desmoplastic in 27 and not specified in 3; it was classic in 44/54 children, nodular/desmoplastic in 9, and with extensive nodularity in one (who was 4 years-old at diagnosis) (P < 0.00001). In 70% of cases, lateral tumors were histologically desmoplastic/nodular. Molecular subgrouping of tumors was available for a few patients, i.e. 29 adults (28 SHH subgroup and one non WNT/non SHH), and 6 children (2 WNT, 1 SHH and 3 non SHH/non WNT).

Treatment

Thirty-six adults had CSI at total doses of 23.4 Gy, and 8 received 30.6 Gy. As far the boosts, 23/44 adults and 35/54 children had a boost to the PF, while 21 adults and the other 19 children had a boost to the TB. In Milano, from 2006 to 2014, all patients received CSI and PF/TB boosts with a 3D-conformal technique. In 2014, a volumetric modulated arc therapy (VMAT) technique was adopted for the boosts, and since February 2016 a VMAT technique was adopted also for CSI. Both CSI techniques were delivered using a moving junction strategy.

Forty-three of the 44 adults also had chemotherapy. Some were given carboplatin/etoposide for 2 courses (in 7 cases), or the eight-in-one schedule for 2 courses (in 3 cases) prior to RT, then carboplatin/etoposide for 2 courses (in 11 patients) or the eight-in-one schedule for 2 courses (in 10) after RT. The other 22 patients not given chemotherapy before RT were given lomustine, vincristine, and cisplatin or carboplatin afterwards for a maximum of 8 courses (Table 1). The only patient not given chemotherapy had a total CSI of 30.6 Gy. All 54 children were treated after surgery with 23.4 Gy CSI plus a boost to the PF or TB as specified above at a total dose of 54 Gy, followed by up to 8 courses with lomustine, vincristine, and cisplatin or carboplatin.

Given the homogeneous post-RT regimen used in 22 adults and 54 children, we calculated the feasibility of this approach to the treatment of both adults and children, as far as the use of lomustine and cisplatin are concerned. The median number of full doses of lomustine administered was 8 (range 6–8) for the adults and 8 (range 8–8) for the children. The median number of full doses of cisplatin administered was 6 (range 5–8) for the adults and 5 (range 4–8) for the children. The median cumulative dose of cisplatin was 420 mg/m^2 (range 350–560) in the adults and 385 mg/m^2 (range 280–560) in the children (P ns). Data on dose intensity, acute neurotoxicity, ototoxicity and nephrotoxicity were also compared between the two groups, revealing no significant differences (data not shown).

Survival analyses

For the 44 adults, the PFS and OS at 5 years were 82.2 ± 6.1% and 89 ± 5.2%, respectively, and at 10 years they were 78.5 ± 6.9% and 75.21 ± 7.8%. The median time to progression was 44 months (range 15–82). For the 54 children, the PFS and OS at 5 years were 94.2 ± 3.3% and 100%, respectively, and at 10 years they were 91.8 ± 4% and 84.5 ± 6.6%. The median time to progression in this group was 49 months (mean 36 months). Figures 1 and 2 show the PFS and OS in the two patient groups. The differences between the two populations were not significant for PFS or OS.

Among the adults, neither the doses of CSI nor any use of pre-RT chemotherapy, or the type of post-RT schedule had any influence on the patients' PFS or OS. The only patient not given any chemotherapy did not relapse.

The female adult patients tended to have a better PFS and OS than the males. The PFS at both 5 and 10 years was 94.4 ± 5.4% for females as opposed to 72.7 ± 9.5% and 66.7 ± 10.5% for males (P = 0.0580). The OS at 5 and 10 years was 100% and 91.7 ± 8% for females as opposed to 81.1 ± 8.59% and 64.5 ± 11% for males (P = 0.0753).

In all, there were 12 patients who relapsed, 8 adults and 4 children. The relapses in adults were local in 4 cases, local + the CSF, spine or bone in one case each, and only in bone in one. The relapses in children were local in 2 cases, with leptomeningeal dissemination in one, and with a single metastatic nodule in one. There was no statistically significant difference in the local component of relapse between the two groups. When the different extent of the boost was considered, however, all 6 relapsing patients for whom data were available (including the 4 with a component of local relapse, of course) had received a boost to the PF (P = 0.1580). One child developed a cerebellar glioblastoma 85 months after receiving irradiation, and died 18 months later.

Long-term toxicity

Tables 2 and 3 show the late effects, as documented in the clinical records, of 22 adult patients and 49 children.

Endocrine problems were identified in 53% of the adults and 97% of the children tested. They mainly involved hypothyroidism and vitamin D deficiency in both groups. Thyroid nodules were more common in adults (47% vs 19%) (P = 0.021). Ototoxicity came to light in 47% of the adults and 67% of the children (P = 0.0513). Some degree of alopecia was evident in 20% of the adults and 29% of the children. Cerebellar impairment, always as a persistent consequence of surgical excisions, was recorded in 60% of the adults tested and 17% of the children (P = 0.000).

Table 1 Adult series treatment and outcome

Patient #	Institute	Sex	Time of diagnosis	Age at diagnosis	Complete surgery	Histological subtype	Dose CSI	Boost PF/TB	CT pre-RT	CT post-RT	OS months	Status	Present life
1	INT-Milano	M	05/06/2006	23	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	50	DOD	
2	INT-Milano	F	28/06/2006	20	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	164	CCR	University Board. Full-time work. Sports
3	INT-Milano	F	07/03/2008	21	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	140	CCR	Busche. engaged
4	INT-Milano	M	30/06/2008	39	Yes	Nodular/desmoplastic	23.4	PF	No	CDPP/VCR/CCNU	137	CCR	Teacher. married, smoker. no sports
5	INT-Milano	M	05/09/2008	23	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	131	CCR	University board as engeneer. engaged. sports
6	INT-Milano	M	07/02/2010	30	Yes	Nodular/desmoplastic	23.4	PF	No	CDPP/VCR/CCNU	69	DOD	
7	INT-Milano	F	02/11/2010	20	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	108	CCR	Employed. one daughter
8	INT-Milano	F	07/09/2011	26	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	90	CCR	University Board. married
9	INT-Milano	F	02/12/2011	20	Yes	Classic	23.4	PF	No	CDPP/VCR/CCNU	98	CCR	University board. Employed. Engaged. sports
10	INT-Milano	F	15/11/2011	32	Yes	Nodular/desmoplastic	23.4	PF	No	CDPP/VCR/CCNU	91	CCR	Teacher. Married. one son. sports
11	INT-Milano	M	15/11/2012	23	Yes	Nodular/desmoplastic	23.4	PF	No	CDPP/VCR/CCNU	84	CCR	Employed. lives alone
12	INT-Milano	F	17/10/2013	22	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	72	CCR	Looking for a job
13	INT-Milano	F	10/07/2014	30	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	41	CCR	One child after treatment. lives in own family
14	INT-Milano	F	27/11/2014	33	No	Nodular/desmoplastic	23.4	PF	No	CDPP/VCR/CCNU	31	CCR	Stop smoking.own family
15	INT-Milano	M	27/01/2015	20	Yes	Classic	23.4	TB	No	CDPP/VCR/CCNU	57	CCR	Married. public employment. sports
16	INT-Milano	F	07/04/2015	18	Yes	Classic	23.4	TB	No	CDPP/VCR/CCNU	57	CCR	University student. sports. some mood alteration

Table 1 (continued)

Patient #	Institute	Sex	Time of diagnosis	Age at diagnosis	Complete surgery	Histological subtype	Dose CSI	Boost PF/TB	CT pre-RT	CT post-RT	OS months	Status	Present life
17	INT-Milano	F	26/01/2016	29	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	48	CCR	Employed. engaged
18	INT-Milano	F	15/02/2016	21	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	49	CCR	University board. Engaged. sports
19	INT-Milano	M	25/02/2016	40	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	47	CCR	Employed. agonistic sport
20	INT-Milano	F	17/11/2016	44	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR—VCR/EDX per 6 cicli	47	CCR	Employed. already married and mother
21	INT-Milano	M	08/03/2018	48	Yes	Nodular/Desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	25	CCR	Own job. own family
22	INT-Milano	F	20/06/2018	29	Yes	Nodular/desmoplastic	23.4	TB	No	CDPP/VCR/CCNU	20	CCR	University board. looking for a job
23	CLB-Lyon	M	17/02/2014	20	Yes	Classic	23.4	TB	No	2 courses eight-in-one	29	CCR	
24	CLB-Lyon	M	15/10/2003	18	Yes	Classic	23.4	PF	2 courses eight-in -one	2 courses eight-in-one	194	CCR	
25	CLB-Lyon	M	04/02/2015	21	Yes	Classic	23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	37	DOD	
26	CLB-Lyon	M	13/01/2010	25	Yes	Nodular/desmoplastic	23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	105	CCR	
27	CLB-Lyon	F	05/02/2014	26	Yes	Nodular/desmoplastic	23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	68	CCR	
28	CLB-Lyon	M	23/12/2012	27	Yes		23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	70	CCR	
29	CLB-Lyon	M	06/05/2014	29	Yes	Nodular/desmoplastic	23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	70	CCR	
30	CLB-Lyon	M	22/01/2010	30	Yes		23.4	TB	2 courses eight-in-one	2 courses eight-in-one	120	CCR	
31	CLB-Lyon	M	19/01/2009	30	Yes	Nodular/desmoplastic	23.4	TB	no	2 courses eight-in-one	103	DOD	
32	CLB-Lyon	M	07/09/2010	31	Yes	Classic	23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	111	CCR	
33	CLB-Lyon	M	04/02/2011	32	Yes	Nodular/desmoplastic	23.4	TB	2 courses Carbo/VP	2 courses eight-in-one	106	CCR	
34	CLB-Lyon	F	23/11/2007	34	Yes	Nodular/desmoplastic	23.4	TB	No	2 courses eight-in-one	69	DOD	

Table 1 (continued)

Patient #	Institute	Sex	Time of diagnosis	Age at diagnosis	Complete surgery	Histological subtype	Dose CSI	Boost PF/TB	CT pre-RT	CT post-RT	OS months	Status	Present life
35	CLB-Lyon	F	11/06/1999	40	Yes		23.4	PF	No	2 courses eight-in-one	219	CCR	Dementia
36	CLB-Lyon	M	14/02/2006	48	Yes	Nodular/desmoplastic	23.4	PF	No	2 courses eight-in-one	141	CCR	
37	CLB-Lyon	M	15/04/1996	26	Yes		30	PF	2 courses eight-in-one	2 courses eight-in-one	227	CCR	
38	CLB-Lyon	M	15/04/2000	21	Yes	Nodular/desmoplastic	30.6	PF	no	2 courses eight-in-one	197	CCR	
39	CLB-Lyon	M	15/05/2000	19	Yes	Nodular/desmoplastic	30.6	PF	no	2 courses eight-in-one	63	DOD	
40	CLB-Lyon	M	15/07/2000	23	Yes	Classic	30.6	PF	no	2 courses eight-in-one	48	DOD	
41	CLB-Lyon	F	15/08/2000	34	Yes	Nodular/desmoplastic	30.6	PF	No	2 courses eight-in-one	179	CCR	
42	CLB-Lyon	F	15/04/2001	39	Yes	Nodular/desmoplastic	30.6	PF	No	2 courses eight-in-one	220	CCR	
43	CLB-Lyon	M	15/08/2001	28	Yes	Nodular/desmoplastic	30.6	PF	No	2 courses eight-in-one	50	DOD	
44	CLB-Lyon	F	15/09/2003	30	Yes	Nodular/desmoplastic	30.6	PF	No	No	187	CCR	

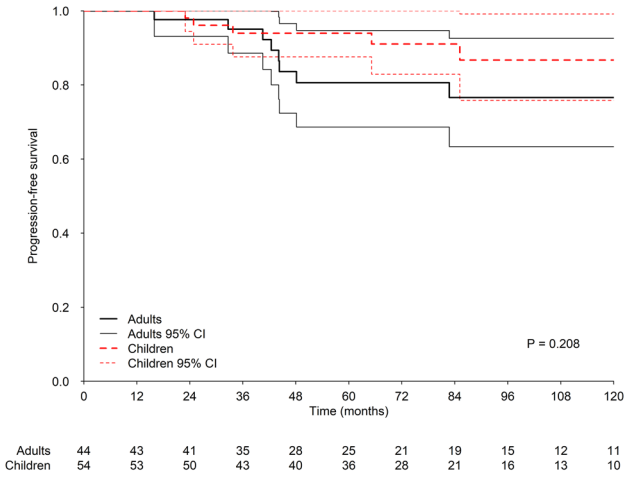

Fig. 1 PFS of adult and children series

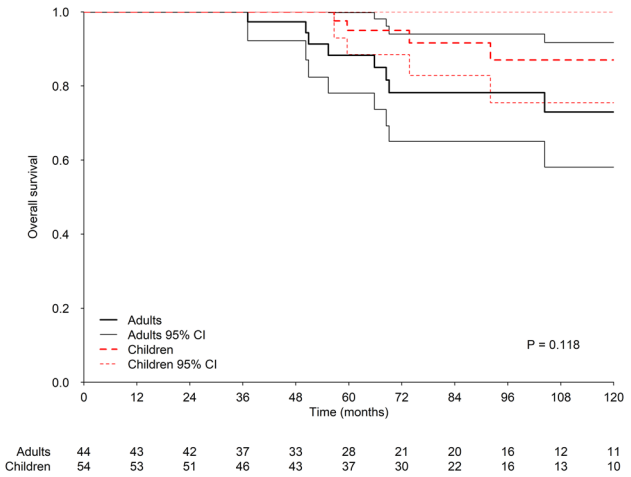

Fig. 2 OS of adult and children series

Discussion

Medulloblastoma treatments in use today achieve OS and EFS rates of up to 85.9% and 82.6%, respectively, at 5 years, in children with MB classified as average-risk (or standard-risk in Europe) [11, 12].

Our understanding of the molecular drivers behind MB has improved considerably now that distinct molecular subgroups have been identified, as well as the known histological subtypes of this disease. This new information is now being incorporated in prospective clinical trials on pediatric MB [13, 14].

For our series of cases treated at two centers, a thorough molecular subtyping was unfeasible for most patients due to the retrospective nature of our analysis. We could however observe a significant majority of lateral location and desmoplastic/nodular histotype in adults as compared to children.

As in MB in children, in adults too we can identify two clinical risk classes depending on metastatic status and the residual dimensions after surgical resection, although the prognostic significance of residual disease is still strongly debated and has yet to be confirmed in adults [15]. For quite a few years now, adults have been treated with resection, if complete followed by conventional full doses CSI.

Table 2 Children late-effects (49 survivors)

Tested	Sequela	Affected	%
42 endocrine alterations	Growth hormone deficit	27	64
	Hypothyroidism	31	74
	Vitamin D deficiency	36	86
	Metabolic syndrome	4	10
	Thyroid nodules	8	19
	None	2	3
46 ototoxicity	Acute tones impairment	26	67
	Prosthesis	5	
	None	15	33
48 alopecia	Alopecia > 30% scalp	3	29
	Thin and reduced hair	6	
	Nuchal alopecia	4	
	None	39	71
48 neurological impairments	Cerebellar syndrome	3	17
	Ocular movements	3	
	Other	2	
	None	40	83

Table 3 Late effects in adults (22/36 survivors—both series)

Tested	Sequelae	Patients affected	%
17 endocrine changes	Growth hormone deficit	2	12
	Hypothyroidism	11	65
	Vitamin D deficiency	6	35
	Metabolic syndrome	5	29
	Thyroid nodules	8	47
	None	1	6
19 ototoxicity	Acute tones impairment	7	47
	Prosthesis	2	
	None	10	53
20 alopecia	Alopecia > 30% scalp	4	20
	None	16	80
22 neurological impairment	Cerebellar syndrome	12	60
	Ocular movements	4	20
	Other	6	20
	None	8	40

Upfront chemotherapy has only been used for patients with incomplete resections and/or metastatic disease [16].

Two large retrospective studies (a National Cancer Data Base analysis and a meta-analysis) [4, 17], and another two prospective protocols [18–20] have recently generated evidence to support the use of upfront chemotherapy and its feasibility in adults. As adjuvant chemotherapy with standard-risk MB, standard-dose CSI can be followed by chemotherapy (lomustine, cisplatin, and vincristine). This solution has reportedly achieved 4-year EFS and OS rates of 68% and 89%, respectively [21]. In an Italian series of 43 standard-risk adult MB patients, the DEC regimen (cisplatin, etoposide, and cyclophosphamide) associated with RT in 15 cases reached a 10-year OS rate of 100% (as compared with 79% for patients only given RT) [22].

Two large retrospective studies found upfront chemotherapy beneficial in standard-risk adult MB patients [4, 17]. A registry from the U.S. National Cancer Data Base returned details of 751 adults (88% with non-metastatic disease) diagnosed from 2004 to 2012 who were given CSI plus adjuvant chemotherapy (69%), or CSI alone (31%) [4]. Analyzing this sample revealed a survival advantage for the combination of chemotherapy and RT after surgery compared with RT alone (with a 5-year OS of 86% as opposed to 72%), even for non-metastatic patients given high doses of CSI. In a meta-analysis Kocakaya et al. showed that chemotherapy improved survival (even though 20% of the sample considered showed signs of metastases) [17]. An international retrospective study on 206 adults (62% with non-metastatic disease) diagnosed between 1976 and 2014 also found that patients given chemotherapy (48% of the cohort) had a better local disease control and longer survival [3].

Importantly, with a combination of chemotherapy (usually with regimens containing platinum), better staging and more scrupulous patient selection, adults with standard-risk MB might be able to benefit from lower doses of CSI, as in childhood [13, 23]. A French study on 253 adults (124 at standard risk) found no differences in survival between patients given CSI at doses > 34 Gy and those given < 34 Gy plus chemotherapy [24]. This finding is supported by an American study on 29 adults, including 7 standard-risk cases given reduced doses of CSI (23.4 Gy) with concurrent and adjuvant chemotherapy; remarkably, none of these patients relapsed [8]. In the German HIT 2000 study, a group of 9 adult standard-risk patients given reduced-dose CSI (23.4 Gy) plus chemotherapy had the same prognosis as 47 patients given CSI alone at doses of 35.2 Gy [21].

The feasibility of using pediatric protocols for adults has sometimes suffered from problems of hematological and neurological toxicity. For instance, a recent phase II study on RT and chemotherapy for adults with MB, the plan was to administer CSI and concurrent vincristine followed by cisplatin, lomustine, and vincristine, but only 70% of the patients received more than 4 cycles of this regimen, and they all needed dose reductions [20].

Our report shows that adults are able to tolerate chemotherapy for MB just as well as children, and that a lower dose of CSI can be administered without impairing the outcome. We also found that the dosage of cisplatin and lomustine was comparable in our two age groups, confirming that the related toxicity was no more severe in adults.

Interestingly, none of the adults for whom details of the extent of their boost extension were available in our records relapsed locally after a boost to the TB. This finding confirms that, with adequate staging, a boost to the whole PF is no more necessary in adults with MB than it is in children.

Our results for adult MB compare fairly well with the recent literature and are satisfactory even in the longer term needed to reveal late relapses—which are more common in adults than in children [25]. Reducing the dose of CSI for adults is likely to favorably affect their neurocognitive outcome and quality of life [2, 26]. For children with standard-risk MB, it has recently been established that 23.4 Gy is the lower threshold dose of CSI (combined with chemotherapy) below which it is unwise to go, barring extremely particular situations [11, 12, 23]. We do not know what the lower threshold dose might be for adults, and we can only guess at whether it might differ from that of pediatric MB with the same histology and biological characteristics.

In our long-term assessment of late effects, adults experienced no more ototoxicity or nephrotoxicity than children. They did develop more thyroid nodules, partly due to the effects of aging [27]. Adults were also neurologically more impaired, and more persistently so after surgery, probably as a result of a declining neuroplasticity with aging [28] and/or to differences in their rehabilitation, which usually lasts longer in children [29]. We did not have enough data on our adult patients' fertility, but the long life expectancy makes it necessary to provide for the cryopreservation of patients' gametes, and most of the patients described herein were offered the opportunity to do so.

The European SIOP PNET-5 trial (underway since 2014) is reducing the total doses cisplatin and lomustine chemotherapy vis-à-vis the PNET-4 trial, which was our schedule adopted in most patients [30]. Late effects should be lessened, and this same approach could be proposed to adults in similar clinical (and molecular) risk groups too [31].

Acknowledgements Associazione Bianca Garavaglia, Busto Arsizio; LILT (Lega Italiana per la Lotta contro i Tumori), Milano; Con Lorenzo per mano Onlus, Como; Bimbo Tu Onlus, Bologna

Funding Associazione Bianca Garavaglia, Busto Arsizio; LILT (Lega Italiana per la Lotta contro i Tumori), Milano; Con Lorenzo per mano Onlus, Como; Bimbo Tu Onlus, Bologna.

Compliance with ethical standards

Conflict of interest None to be declared by any of the authors.

References

1. Merchant TE, Pollack IF, Loeffler JS (2010) Brain tumors across the age spectrum: biology, therapy, and late effects. Semin Radiat Oncol 20:58–66. https://doi.org/10.1016/j.semradonc.2009.09.005
2. Majd N, Penas-Prado M (2019) Updates on management of adult medulloblastoma. Curr Treat Options Oncol 20:64–24. https://doi.org/10.1007/s11864-019-0663-0
3. Atalar B, Ozsahin M, Call J, Napieralska A, Kamer S, Villa S, Erpolat P, Negretti L, Lassen-Ramshad Y, Onal C, Akyurek S, Ugurluer G, Baumert BG, Servagi-Vernat S, Miller RC, Ozyar E, Sio TT (2018) Treatment outcome and prognostic factors for adult patients with medulloblastoma: the Rare Cancer Network (RCN) experience. Radiother Oncol 127:96–102. https://doi.org/10.1016/j.radonc.2017.12.028
4. Kann BH, Lester-Coll NH, Park HS, Yeboa DN, Kelly JR, Baehring JM, Becker KP, Yu JB, Bindra RS, Roberts KB (2017) Adjuvant chemotherapy and overall survival in adult medulloblastoma. Neuro-Oncology 19:259–269
5. Juraschka K, Taylor MD (2019) Medulloblastoma in the age of molecular subgroups: a review. J Neurosurg 24:353–363. https://doi.org/10.3171/2019.5.peds18381
6. Remke M, Hielscher T, Northcott PA, Witt H, Ryzhova M, Wittmann A, Benner A, von Deimling A, Scheurlen W, Perry A, Croul S, Kulozik AE, Lichter P, Taylor MD, Pfister SM, Korshunov A (2011) Adult medulloblastoma comprises three major molecular variants. J Clin Oncol 29:2717–2723. https://doi.org/10.1200/JCO.2011.34.9373
7. Carrie C, Lasset C, Alapetite C, Maire JP, Haie-Meder C, Hoffstetter S et al (1994) Multivariate analysis of prognostic factors in adult patients with medulloblastoma. Retrospective study of 156 patients. Cancer 74:2352–2360. https://doi.org/10.1002/1097-0142(19941015)74:8<2352:AID-CNCR2820740821>3.0.CO;2-H
8. De B, Beal K, De Braganca KC, Souweidane MM, Dunkel IJ, Khakoo Y, Gilheeney SW, DeAngelis LM, Menzel P, Patel SH, Wolden SL (2018) Long-term outcomes of adult medulloblastoma patients treated with radiotherapy. J Neurooncol 136:95–104. https://doi.org/10.1007/s11060-017-2627-1
9. Gentet JC, Bouffet E, Doz F, Tron P, Roche H, Thyss A, Plantaz D, Stephan JL, Mottolese C, Ponvert D, Carrie C, Raybaud C, Brunat-Mentigny M, Choux M, PhilipZucker TJM, Bernard JL (1995) Preirradiation chemotherapy including "eight drugs in 1 day" regimen and high-dose methotrexate in childhood medulloblastoma: results of the M7 French Cooperative Study. J Neurosurg 82:608–614. https://doi.org/10.3171/jns.1995.82.4.0608
10. Gentet JC, Doz F, Bouffet E, Plantaz D, Roché H, Tron P, Kalifa C, Mazingue F, Sariban E, Chastagner P et al (1994) Carboplatin and VP 16 in medulloblastoma: a phase II Study of the French Society of Pediatric Oncology (SFOP). Med Pediatr 23:422–427. https://doi.org/10.1002/mpo.2950230506
11. Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, Navajas A, Massimino M, Reddingius R, Benesch M, Carrie C, Taylor R, Gandola L, Björk-Eriksson T, Giralt J, Oldenburger F, Pietsch T, Figarella-Branger D, Robson K, Forni M, Clifford SC, Warmuth-Metz M, von Hoff K, Faldum A, Mosseri V, Kortmann R (2012) Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol 30:3187–93. https://doi.org/10.1200/JCO.2011.39.8719
12. Michalski JM, Janss A, Vezina G, Gajjar A, Pollack I, Merchant TE et al (2016) Results of COG ACNS0331: a phase III trial of involved-field radiotherapy (IFRT) and low-dose craniospinal irradiation (LD-CSI) with chemotherapy in average-risk medulloblastoma: a report from the Children's Oncology Group, ASTRO meeting 2016. Int J Radiat Oncol Biol Phys 5:937–938
13. Northcott PA, Robinson GW, Kratz CP, Mabbott DJ, Pomeroy SL, Clifford SC et al (2019) Medulloblastoma. Nat Rev Dis Primers 5(1):11. https://doi.org/10.1038/s41572-019-0063-6
14. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B et al (2017) Intertumoral heterogeneity within medulloblastoma subgroups. Cancer Cell 31:737–754.e6. https://doi.org/10.1016/j.ccell.2017.05.005
15. Brandes AA, Bartolotti M, Marucci G, Ghimenton C, Agati R, Fioravanti A, Mascarin M, Volpin L, Ammannati F, Masotto B, Gardiman MP, de Biase D, Tallini G, Crisi G, Bartolini S, Franceschi E (2015) New perspectives in the treatment of adult medulloblastoma in the era of molecular oncology. Crit Rev Oncol/Hematol 94:348–359. https://doi.org/10.1016/j.critrevonc.2014.12.016
16. Brandes AA, Franceschi E, Tosoni A, Frezza G, Agati R, Maestri A et al (2010) Efficacy of tailored treatment for high- and low-risk medulloblastoma in adults: a large prospective phase II trial. J Clin Oncol 28:2003–2003. https://doi.org/10.1200/jco.2010.28.15_suppl.2003
17. Kocakaya S, Beier CP, Beier D (2016) Chemotherapy increases long-term survival in patients with adult medulloblastoma-a literature-based meta-analysis. Neuro-Oncology 18:408–416. https://doi.org/10.1093/neuonc/nov185
18. Brandes AA, Ermani M, Amista P, Basso U, Vastola F, Gardiman M et al (2003) The treatment of adults with medulloblastoma: a prospective study. Int J Radiat Oncol Biol Phys 57:755–761. https://doi.org/10.1016/S0360-3016(03)00643-6
19. Brandes AA, Franceschi E, Tosoni A, Blatt V, Ermani M (2007) Long-term results of a prospective study on the treatment of medulloblastoma in adults. Cancer 110:2035–2041. https://doi.org/10.1002/cncr.23003
20. Beier D, Proescholdt M, Reinert C, Pietsch T, Jones DTW, Pfister SM, Hattingen E, Seidel C, Dirven L, Luerding R, Reijneveld J, Warmuth-Metz M, Bonsanto M, Bremer M, Combs SE, Rieken S, Herrlinger U, Kuntze H, Mayer-Steinacker R, Moskopp D, Schneider T, Beringer A, Schlegel U, Stummer W, Welker H, Weyerbrock A, Paulsen F, Rutkowski S, Weller M, Wick W, Kortmann RD, Bogdahn U, Hau P (2018) Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). Neuro-Oncology 20:400–410. https://doi.org/10.1093/neuonc/nox155
21. Friedrich C, Von Bueren AO, Von Hoff K, Kwiecien R, Pietsch T, Warmuth-Metz M et al (2013) Treatment of adult nonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: a prospective observational multicentre study. Eur J Cancer 49:893–903. https://doi.org/10.1016/j.ejca.2012.10.006
22. Franceschi E, Bartolotti M, Paccapelo A, Marucci G, Agati R, Volpin L, Danieli D, Ghimenton C, Gardiman MP, Sturiale C, Poggi R, Mascarin M, Balestrini D, Masotto B, Brandes AA (2016) Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients? J Neurooncol 128:235–240. https://doi.org/10.1007/s11060-016-2097-x
23. Massimino M, Biassoni V, Gandola L, Garrè ML, Gatta G, Giangaspero F et al (2016) Childhood medulloblastoma. Crit Rev Oncol/Hematol 105:35–51. https://doi.org/10.1016/j.critrevonc.2016.05.012
24. Padovani L, Sunyach MP, Perol D, Mercier C, Alapetite C, Haie-Meder C et al (2007) Common strategy for adult and pediatric

medulloblastoma:a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys 68:433–440. https://doi.org/10.1016/j.ijrobp.2006.12.030
25. Herrlinger U, Steinbrecher A, Rieger J, Hau P, Kortmann R, Meyermann R, Schabet M, Bamberg M, Dichgans J, Bogdahn U, Weller M (2005) Adult medulloblastoma: prognostic factors and response to therapy at diagnosis and at relapse. J Neurol 252:291–299
26. Harrison RA, Kesler SR, Johnson JM, Penas-Prado M, Sullaway CM, Wefel JS (2019) Neurocognitive dysfunction in adult cerebellar medulloblastoma. Psycho-Oncology 28:131–138. https://doi.org/10.1002/pon.4920
27. Kwong N, Medici M, Angell TE, Liu X, Marqusee E, Cibas ES, Krane JF, Barletta JA, Kim MI, Larsen PR, Alexander EK (2015) The influence of patient age on thyroid nodule formation, multinodularity, and thyroid cancer risk. J Clin Endocrinol Metab 100:4434–4440. https://doi.org/10.1210/jc.2015-3100
28. Sophie Su YR, Veeravagu A, Grant G (2016) Neuroplasticity after traumatic brain injury. In: Laskowitz D, Grant G (eds) Translational research in traumatic brain injury. CRC Press/Taylor and Francis Group, Boca Raton
29. Fischer C, Petriccione M, Donzelli M, Pottenger E (2016) Improving care in pediatric neuro-oncology patients: an overview of the unique needs of children with brain tumors. J Child Neurol 31:488–505. https://doi.org/10.1177/0883073815597756
30. https://clinicaltrials.gov/ct2/show/study/NCT02066220
31. Franceschi E, Hofer S, Brandes AA, Frappaz D, Kortmann RD, Bromberg J, Dangouloff-Ros V, Boddaert N, Hattingen E, Wiestler B, Clifford SC, Figarella-Branger D, Giangaspero F, Haberler C, Pietsch T, Pajtler KW, Pfister SM, Guzman R, Stummer W, Combs SE, Seidel C, Beier D, McCabe MG, Grotzer M, Laigle-Donadey F, Stücklin ASG, Idbaih A, Preusser M, van den Bent M, Weller M, Hau P (2019) EANO-EURACAN clinical practice guideline for diagnosis, treatment, and follow-up of post-pubertal and adult patients with medulloblastoma. Lancet Oncol 20:e715–e728. https://doi.org/10.1016/S1470-2045(19)30669-2

Affiliations

Maura Massimino[1] · Marie Pierre Sunyach[2] · Francesco Barretta[3] · Lorenza Gandola[4] · Anna Garegnani[5] · Emilia Pecori[4] · Filippo Spreafico[1] · Alice Bonneville-Levard[6] · David Meyronet[7] · Carmine Mottolese[8] · Luna Boschetti[1] · Veronica Biassoni[1] · Elisabetta Schiavello[1] · Carlo Giussani[9] · Giorgio Carrabba[10] · Barbara Diletto[4] · Federica Pallotti[11] · Roberto Stefini[12] · Andrea Ferrari[1] · Monica Terenziani[1] · Michela Casanova[1] · Roberto Luksch[1] · Cristina Meazza[1] · Marta Podda[1] · Stefano Chiaravalli[1] · Nadia Puma[1] · Luca Bergamaschi[1] · Carlo Morosi[16] · Giuseppina Calareso[16] · Felice Giangaspero[13,14] · Manila Antonelli[13] · Francesca Romana Buttarelli[15] · Didier Frappaz[6]

1 Pediatric Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Via Venezian 1, 20133 Milan, Italy

2 Radiotherapy Department, Centre Léon Bérard, Lyon, France

3 Clinical Epidemiology and Trial Organization Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy

4 Pediatric Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Via Venezian 1, 20133 Milan, Italy

5 Milan, Italy

6 Neuro-Oncology, Centre Léon Bérard, Lyon, France

7 Pathology Department, Centre Hospitalo-Universitaire, Lyon, France

8 Neurosurgery Department, Centre Hospitalo-Universitaire, Lyon, France

9 Neurosurgery Unit, University of Milano-Bicocca, Ospedale San Gerardo, Monza, Italy

10 Neurosurgery Unit, Ospedale Policlinico Ca' Granda, Milano, Italy

11 Nuclear Medicine Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy

12 Neurosurgery Unit, Legnano Hospital, Milan, Italy

13 Department of Radiological, Oncological and Anatomo-Pathological Sciences, Sapienza University, Rome, Italy

14 Pathology Department, IRCCS Neuromed, Pozzilli, Italy

15 Neurological Science, Sapienza University, Roma, Italy

16 Radiology Department, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy