J Neurooncol
DOI 10.1007/s11060-016-2097-x

CLINICAL STUDY

Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients?

E. Franceschi[1] · M. Bartolotti[1] · A. Paccapelo[1] · G. Marucci[2] · R. Agati[3] · L. Volpin[4] · D. Danieli[5] · C. Ghimenton[6] · M. P. Gardiman[7] · C. Sturiale[8] · R. Poggi[1] · M. Mascarin[9] · D. Balestrini[10] · B. Masotto[11] · A. A. Brandes[1]

Received: 23 September 2015 / Accepted: 28 February 2016

Abstract The standard treatment in children with average-risk medulloblastoma (MB) is reduced-dose radiotherapy (RT) followed by chemotherapy. However, in adults, there is no agreement on the use of adjuvant chemotherapy. We performed a retrospective analysis of adult MB patients with average-risk disease, defined as no postsurgical residual (or $\leq$1.5 cm^2) and no metastatic disease (M0). Main inclusion criteria were: age >16 years, post-surgical treatment with craniospinal irradiation with or without adjuvant chemotherapy (cisplatin and etoposide ± cyclophosphamide). From 1988 to 2012 were accrued 43 average-risk MB patients treated with surgery and adjuvant RT. Fifteen (34.9 %) patients received also chemotherapy: 7 before RT, 5 after RT, and 3 before and after RT. Reasons to administer chemotherapy were presence of residual disease (even if $\leq$1.5 cm) and delay in RT. After a median follow up time of 10 years (range: 8–13), median survival was 18 years (95 % CI 9–28) in patients who receive RT alone, and was not reached in patients treated with RT plus chemotherapy. The survival rates at 5, 10 and 15 years were 100 %, 78.6 % (95 % CI 60.0–97.2 %) and 60.2 % (95 % CI 36.9–83.5 %), in patients treated with RT alone, and 100, 100 and 100 %, in patients treated with RT plus chemotherapy (p = 0.079). Our findings suggest a role for adjuvant chemotherapy in the treatment of average-risk MB adult patients. Further improvements might drive to add chemotherapy in

✉ A. A. Brandes
alba.brandes@yahoo.it

E. Franceschi
enricofra@yahoo.it

M. Bartolotti
m.bartolotti@ausl.bologna.it

A. Paccapelo
a.paccapelo@ausl.bologna.it

G. Marucci
gianluca.marucci@ausl.bologna.it

R. Agati
raffaele.agati@ausl.bologna.it

L. Volpin
segreteria.neurochirurgia@ulssvicenza.it

D. Danieli
daniela.danieli@ulssvicenza.it

C. Ghimenton
claudio.ghimenton@ospedaleuniverona.it

M. P. Gardiman
marinapaola.gardiman@sanita.padova.it

C. Sturiale
carmelo.sturiale@ausl.bologna.it

R. Poggi
pogg1@ausl.bologna.it

M. Mascarin
mascarin@cro.it

D. Balestrini
d.balestrini@ausl.bologna.it

[1] Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Via Altura, 3, 40139 Bologna, Italy

[2] Section of Pathology "M. Malpighi", Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Via Altura, 3, 40139 Bologna, Italy

[3] Department of Neuroradiology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Via Altura, 3, 40139 Bologna, Italy

[4] Department of Neuroscience and Neurosurgery, San Bortolo Hospital, Viale Rodolfi, 37, 36100 Vicenza, Italy

Published online: 03 March 2016

average-risk setting with less favourable biological signatures (i.e., non-WNT group).

Keywords Medulloblastoma · Adults · Radiotherapy · Chemotherapy · Average risk

Background

Medulloblastoma is an embryonal tumor of the cerebellum and represents the most common malignant neoplasm of the central nervous system (CNS) in children. It accounts for 15–25 % of all childhood CNS neoplasms and its incidence is estimated being 1:100,000 cases. Medulloblastoma is rare in adults, (less than 1 % of primitive CNS tumors) with an incidence of 0.6–1 case per million per year [1].

Medulloblastoma is potentially a curable disease and current treatments allow 5-year overall survival (OS) rate of up to 75 % [2].

The treatment for average risk of medulloblastoma in adults is represented by surgical resection followed by RT (36 Gy in 20 fractions, followed by a boost of 18 Gy in 10 fractions to the posterior fossa, up to a total of 54 Gy), adding chemotherapy for high-risk patients [2, 3]. The treatment choice is driven by the stratification of the patients into two subgroups of risk, according to the Chang's staging system: average and high-risk [4]. This distinction depends on the extension of the primary tumor (T stage), presence of metastases (M stage) and residual disease ($\geq$1.5 cm^2). T3b and T4 stage historically defined a disease belonging to the high-risk group; however, the prognostic value of T stage is nowadays matter of debate. Many studies on pediatric medulloblastoma did not consider the T stage in the risk stratification, which was based only on the presence or absence of metastatic disease [5, 6]. Another open question is about the prognostic value of large cells/anaplastic histology. Even if histology is not part of the risk stratification, at present, this histotype is frequently considered as a criterion for the inclusion of the patients in the high-risk group.

Given the long life expectancy, one of the major concerns about the treatment of pediatric medulloblastoma is the development of long term toxicity related to RT. For this reason efforts were made in order to reduce RT doses delivered to the CNS of children with average-risk medulloblastoma. To date, following the results of the trials by Packer et al. [5, 6] the standard treatment is chemotherapy (adjuvant lomustine, vincristine, and cisplatin) after reduced-dose RT (23.4 Gy of craniospinal irradiation and a posterior fossa boost to 55.8 Gy) concomitantly with vincristine [5, 6].

However, the role of chemotherapy for adult patients with average-risk medulloblastoma remains, to date, controversial. In fact in adults, RT provides with good disease control, but there is concern regarding the risk of secondary neoplasm and prolonged myelosuppression following chemotherapy. Furthermore, given the rarity of the disease in adults, accrual in clinical trials is difficult and for these reasons, the role of chemotherapy in this risk class is not sufficiently investigated.

In literature, only one prospective trial and one retrospective study addressing the issue of treatment of average-risk adult medulloblastoma can be found [2, 3, 7]. In particular, in this trial, patients with average-risk disease, treated with RT alone had a 5-years progression free survival (PFS) rate of 72 % and a 5-years OS rate of 75 % [2]. To date there is no direct comparison between RT alone and the addition of chemotherapy. Despite the good prognosis, about 25 % of average-risk adult patients eventually die of the disease [2]. Therefore, the question whether it is possible to improve these results with the addition of chemotherapy remains open.

We performed an analysis on our Institutional data warehouse on consecutive adult patients with average-risk medulloblastoma treated with RT alone or RT plus chemotherapy in order to explore the outcome.

Materials and methods

Inclusion criteria were: age >16 years old; post surgical treatment with RT with or without chemotherapy.

Average risk is now defined as no postsurgical residual (or $\leq$1.5 cm^2), and no metastatic disease (M0).

However, for many years average risk patients were defined as no postsurgical residual (or $\leq$1.5 cm^2), no metastatic disease (M0), and T1 to T3a disease.

[5] Pathology Department, San Bortolo Hospital, Viale Rodolfi, 37, 36100 Vicenza, Italy

[6] Pathology Department, Verona Hospital, P.le A. Stefani 1, 37126 Verona, Italy

[7] Surgical Pathology & Cytopathology Unit, Department of Medicine (DIMED), University Hospital, Via Giustiniani, 1, 35121 Padua, Italy

[8] Department of Neurosurgery, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Via Altura, 3, 40139 Bologna, Italy

[9] Department of Radiotherapy Unit, CRO, Via Franco Gallini, 233081 Aviano, Italy

[10] Department of Radiotherapy, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Via Altura, 3, 40139 Bologna, Italy

[11] Department of Neurosurgery, Verona Hospital, P.le A. Stefani 1, 37126 Verona, Italy

Thus, some patients were considered as high risk if presenting with T3b or T4 disease, and thus were treated with surgery, radiotherapy and chemotherapy.

In our data warehouse these patients are now categorized as average risk patients, and thus included in this study.

Lumbar CSF was performed when spine MRI was negative. After surgery CT scan with contrast enhancement was routinely used to define residual disease. MRI of the brain was obtained in all the patients before and 72 h after surgery, and whenever possible, also the MRI of the spine was performed before surgery. In some cases (i.e., emergency surgery for endocranial hypertension) the spine MRI was performed after surgery.

As per Institutional protocol, [2, 7] administered RT was 36 Gy on the cranial-spinal axis in 20 fractions plus a boost on the posterior cranial fossa of 18 Gy in 10 fractions (54 Gy total). Chemotherapy was cisplatin (25 mg/m^2 on days 1–4) plus etoposide 40 mg/m^2 on days 1–4), with or without cyclophosphamide (1000 mg/m^2 on day 4) (DEC regimen).

Chemotherapy could be administered before, after or before and after RT.

Local Ethic Committee gave its approval for the purposes of a chart review and data collection on medulloblastoma patients.

Statistical analysis

Data are reported as means, ranges and frequencies. The Fisher's exact and Kruskal–Wallis tests were applied. Survival data (median survival times together with their 95 % confidence interval) were computed by means of the Kaplan–Meier procedure and were analyzed by means of the log-rank test. Progression-free survival and OS were measured from the time of surgery to first progression or death, respectively, or to the date of the last follow-up. The SPSS (Version 13.0 for Windows; SPSS Inc., Chicago, IL, USA) was used as statistical package. Two-tailed P values less than 0.05 were considered significant

Results

We included one-hundred and fifteen adult patients from 1988 to 2012. Patients characteristics are listed in Table 1.

Median age was 31 years (range: 16–57), M/F ratio 27 (62.8 %)/16 (37.2 %).

Forty-three patients had average-risk disease and were treated with surgery and adjuvant RT. The remaining 72 patients had high risk disease. Among average-risk patients histology was classic in 24 patients (55.8 %), desmoplastic in 12 patients (27.9 %), extensive nodularity in five patients (11.6 %), large cell/anaplastic in two patients (4.7 %).

Fifteen (34.9 %) received also chemotherapy: seven patients before RT, five patients after RT, and three patients both before and after RT.

Reasons to administer chemotherapy were residual disease <1.5 cm in nine patients (60.0 %) and prevision of delay in RT start in six patients (40.0 %).

Median number of chemotherapy cycles was 2 (range: 1–8). Patients treatments are listed in Table 2.

Survival

After a median follow up time of 10 years (95 % CI 8–13), nine patients died, eight for disease progression, one for unknown causes. Relapse sites were spinal canal (four patients), bone (two patients), cerebellum (1) and brain (1). None of these patients received chemotherapy.

In patients who had disease progression, median time to progression was 100 months (range: 19–113). Median post-progression survival in these patients was 41 months (range: 7–114).

Median OS was 18 years (95 % CI 9–28) in patients who received RT alone and not reached in patients treated with RT followed by chemotherapy.

The survival rates at 5, 10 and 15 years were 100 %, 78.6 % (95 % CI 60.0–97.2 %) and 60.2 % (95 % CI 36.9–83.5 %), in patients treated with RT alone, and 100, 100 and 100 %, in those treated with RT plus chemotherapy ($p = 0.079$) (Table 3).

To date, all patients receiving adjuvant chemotherapy are alive (Fig. 1).

Univariate analyses did not show significant differences in survival by gender ($P = 1.000$), age ($P = 0.07$) and T stage (T1-Ta vs. T3b-T4, $P = 0.881$) between groups.

Toxicity

Data on toxicity are available for all patients. Toxicities grades were assigned retrospectively according to CTCAE v4.0. Among all patients receiving chemotherapy, the reported grade ≥3 toxicities were 4 cases of neutropenia (26 %) and one case (6 %) of nausea. Two cases of neutropenia and nausea occurred during pre-RT chemotherapy (all with DEC regimen), while two other cases of neutropenia occurred in patients treated with post RT chemotherapy (one patient treated with cisplatin—VP16 and one with DEC). Out of these, two patients who experienced toxicity with post RT chemotherapy, only one had also received chemotherapy before RT.

Grade ≥3 toxicities related to RT were: a case of hypoacusia (2 %), two cases of G3 neutropenia (4.6 %) and one thrombocytopenia (2 %). None of these patients

Table 1 Patients' characteristics

	Chemotherapy		No chemotherapy		Total	
N	15		28		43	
Mean age	28	(range 16–44)	34	(range 16–57)	31	(range 16–57)
M/F	9/6		18/10		27/16	
Histology						
Classic	8	53.3 %	16	57.1 %	24	51.2 %
Desmoplastic	3	20.0 %	9	32.1 %	12	30.2 %
Extensive nodularity	2	13.3 %	3	10.7 %	5	11.6 %
LCA	2	13.3 %	0	0 %	2	7.0 %
Chemotherapy						
Before RT	7	16.3 %	–	–	7	16.3 %
After RT	5	11.6 %	–	–	5	11.6 %
Before and after RT	3	7.0 %	–	–	3	7.0 %
Reason to administer chemotherapy						
RT delay	6	40 %	–	–	6	14.0 %
Residual disease <1.5 cm^2	9	60 %	–	–	9	20.9 %

Table 2 Patients treatments

Pt number	Age	Reason for chemotherapy	Type of chemotherapy before RT	No. of cycles before RT	Type of chemotherapy after RT	No. of cycles after RT	Relapse
1	22	Residual	DEC	2	DEC	5	No
2	19	Delay	–	–	DEC	1	No
3	40	Delay	DEC	2	–	–	No
4	16	Residual	–	–	Cisplatin- Vp16	6	No
5	21	Residual	–	–	Cisplatin- Vp16	1	No
6	28	Delay	DEC	1	–	–	No
7	35	Delay	–	–	DEC	4	No
8	21	Delay	DEC	1	–	–	No
9	44	Residual	–	–	Cisplatin- Vp16	6	No
10	22	Residual	DEC	2	–	–	No
11	27	Residual	Cisplatin- Vp16	2	Cisplatin- Vp16	4	No
12	29	Residual	DEC	1	–	–	No
13	31	Delay	DEC	2	–	–	No
14	24	Residual	DEC	2	–	–	No
15	41	Residual	DEC	2	DEC	6	No

Table 3 Survival rates according to treatment

	RT alone (n)	RT + chemotherapy (n)	P[a]
5 years-OS	100 % (43)	100 % (15)	0.079
10 years-OS	78.6 % (34)	100 % (15)	
	(95 % CI 60.0–97.2)		
15 years-OS	60.2 % (26)	100 % (15)	
	(95 % CI 36.9–83.5)		

[a] Log-rank test

had received chemotherapy before RT. Grade 1 weight loss (<10 %) was found in four patients (14 %) treated with RT alone and three patients (20 %) treated with RT and chemotherapy. Endocrinopathy (slight increase in TSH and prolactin) was found in a patient treated with RT only [8]. No secondary malignancies were found.

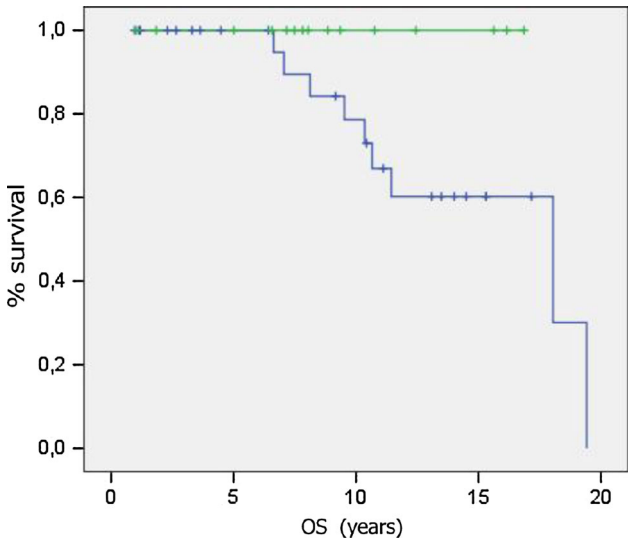

Fig. 1 Survival according to treatment. *Green line* patients treated with adjuvant chemotherapy. *Blue line* patients treated without chemotherapy

Discussion

Medulloblastoma is a rare disease in adult patients and, as a consequence, data about the effectiveness of treatments are limited. To date, adult average risk medulloblastoma is treated with RT only, being the role of chemotherapy still matter of debate. On the contrary, childhood average-risk medulloblastoma is currently treated with a multimodal approach that comprises also chemotherapy. The most important aspect of the addition of chemotherapy in the treatment of children with medulloblastoma is that it allows a reduction of the total dose of RT delivered to the CNS of young patients. This is a key issue, since RT is often burdened with comorbidities that may affect health and quality of life of these patients that are expected to survive their disease.

Our study presents the limitations of a retrospective analysis of a small number of patients, and the potential selection bias of patients. Histology was not reviewed at the time of analysis and thus the designation of anaplasia could be changed throughout the study period. Moreover, we were not able to provide molecular subgroup analysis, thus it is not possible to say whether the survival difference resulted from an imbalanced distribution of more or less aggressive molecular subgroups. However, we showed a potential benefit in terms of increase of survival rates from the addition of chemotherapy in adult patients with average risk medulloblastoma. Indeed, all of the patients treated with both RT and chemotherapy had a 100 % of survival rate at 10 and 15 years, compared with those treated with RT alone [78.6 and 60.2 % at 10 and 15 years ($p = 0.079$)]. The lack of a statistically significant difference in overall survival makes the our findings preliminary, and these data must be considered with caution. Another issue, for which further investigation is warranted, is the possibility to reduce the dose of RT in adult patients receiving chemotherapy. New RT technologies including proton beam craniospinal irradiation decrease acute treatment-related morbidity including fewer acute gastrointestinal and hematologic toxicities in adults with medulloblastoma [9].

An aspect that should be taken into consideration is the tolerance of chemotherapy in adult patients following the RT. In general, after RT, the incidence of hematological and neurological toxicity is higher. In a study by Friedrich et al. [10], in which adult patients were treated according to the HIT 2000 protocol (CCNU, vincristine and cisplatin for eight cycles after RT), the incidence of grade $\geq$3 hematotoxicity was 58 % and grade 2–3 neurotoxicity was 69 %. Half of the patients enrolled managed to receive all the 8 cycles and most of the patients experienced delays and required dose reductions. Therefore, pediatric chemotherapeutic schemes seem unfeasible in adult patients. Chemotherapy seems to be better tolerated when administered before the RT, with an outcome that is similar to that obtained with post-radiation chemotherapy [11, 12]. In our study the incidence of grade $\geq$3 neutropenia was 26 % in all patients who received chemotherapy and 13 % in those who received chemotherapy after RT. These rates are lower than those reported by Friedrich et al. probably due to the fact that regimens like DEC or Cisplatin-VP16 have a better toxicity profile, avoiding nitrosoureas that had significant cumulative hematologic toxicities. Despite the limitations of our study, we suggest that DEC and CDDP-VP16 regimens are more feasible than pediatric protocols in adult patients.

The recent classification of medulloblastoma into molecular subgroups opened the way towards the development of new targeted agents and new risk stratification [13, 14]. Ongoing trials (NCT01878617) are set to determine the efficacy of different treatments, tailored according to the molecular subgroups and the clinical-pathological risk stratification. These studies could answer many questions regarding the optimal treatment that patients should receive according to the characteristics of their disease. From this standpoint, treatment choice for adult average risk medulloblastoma could be influenced, in the next future, by the molecular subgroups [15–18].

Conclusions

Our study showed a potential survival benefit from the addition of chemotherapy after radiation treatment in adult patients with average risk medulloblastoma. Many

questions remain open, such as the optimal schedule and regimen of chemotherapy, the duration and whether chemotherapy should be offered to all patients. Further research could help improving the risk stratification of the patients and the decision making could be influenced by biological signatures.

Authors' contribution EF. conceived the study and participated in its design, coordination and draft. M.B. participated in the coordination and draft of the study. A.P. carried out the statistical analysis. G.M. carried out histopathological diagnosis. R.A. did the neuroradiological evaluations. L.V. performed surgery and provided patients. D.D. carried out histopathological diagnosis. C.G carried out histopathological diagnosis. M.P.G. carried out histopathological diagnosis. C.S. performed surgery and provided patients. R.P. participated in data collection. M.M. provided data about radiotherapy treatment. D.B. provided data about radiotherapy treatment. B.M. performed surgery and provided patients. A.A.B conceived the study and participated in its design, coordination and draft.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interests.

References

1. Smoll NR, Drummond KJ (2012) The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. J Clin Neurosci 19:1541–1544
2. Brandes AA, Franceschi E, Tosoni A et al (2007) Long-term results of a prospective study on the treatment of medulloblastoma in adults. Cancer 110:2035–2041
3. Padovani L, Sunyach MP, Perol D 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
4. Chang CH, Housepian EM, Herbert C Jr (1969) An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology 93:1351–1359
5. Packer RJ, Goldwein J, Nicholson HS et al (1999) Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. J Clin Oncol 17:2127–2136
6. Packer RJ, Gajjar A, Vezina G et al (2006) Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 24:4202–4208
7. Brandes AA, Ermani M, Amista P et al (2003) The treatment of adults with medulloblastoma: a prospective study. Int J Radiat Oncol Biol Phys 57:755–761
8. Brandes AA, Pasetto LM, Lumachi F et al (2000) Endocrine dysfunctions in patients treated for brain tumors: incidence and guidelines for management. J Neurooncol 47:85–92
9. Brown AP, Barney CL, Grosshans DR et al (2013) Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. Int J Radiat Oncol Biol Phys 86(2):277–284
10. Friedrich C, von Bueren AO, von Hoff K 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
11. Kortmann RD, Kuhl J, Timmermann B et al (2000) Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. Int J Radiat Oncol Biol Phys 46:269–279
12. Tarbell NJ, Friedman H, Polkinghorn WR et al (2013) High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol 31:2936–2941
13. Gajjar A, Stewart CF, Ellison DW et al (2013) Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. Clin Cancer Res 19:6305–6312
14. Rodon J, Tawbi HA, Thomas AL et al (2014) A phase 1, multicenter, open-label, first-in-human, dose-escalation study of the oral hedgehog inhibitor Sonidegib (LDE225) in patients with advanced solid tumors. Clin Cancer Res 20:1900
15. Brandes AA, Franceschi E (2014) Shedding light on adult medulloblastoma: current management and opportunities for advances. Am Soc Clin Oncol Educ Book 34:e82-7
16. Brandes AA, Franceschi E (2010) Neuro-oncology: genetic variation in pediatric and adult brain tumors. Nat Rev Neurol 6(12):653–654
17. Brandes AA, Franceschi E, Tosoni A et al (2009) Adult neuroectodermal tumors of posterior fossa (medulloblastoma) and of supratentorial sites (stPNET). Crit Rev Oncol Hematol 71(2):165–179
18. Brandes AA, Paris MK (2004) Review of the prognostic factors in medulloblastoma of children and adults. Crit Rev Oncol Hematol 50(2):121–128