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Survival of adults treated for medulloblastoma using paediatric protocols

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Abstract

We retrospectively studied 26 consecutive adults treated for medulloblastoma using paediatric protocols. Between 1987 and 2003, patients ⩾18 years old were given adjuvant chemotherapy consisting of one of two 'paediatric' regimens (depending on the time of presentation) and craniospinal local-boost radiotherapy: regimen A ($n = 12$), vincristine (VCR), intrathecal and/or intravenous methotrexate and conventional radiotherapy; or regimen B ($n = 11$) sequencing intensive doses of multiple agents followed by hyperfractionated accelerated radiotherapy (HART). A VCR-lomustine-based maintenance followed both regimens. Three additional patients received a tailored treatment due to their impaired neurological status after surgery. The median age at diagnosis was 26 years (range 18–41 years). With a median follow-up of 46 months, 5-year disease-free and overall survival rates were 65 ± 11% and 73 ± 10%, respectively, for the series as a whole. All patients who received regimen B (5 of whom had metastatic Chang M2–M3 disease) are alive with no evidence of disease at 39 months. Although the number of patients is limited, our data suggest that the sandwich sequential, moderately intensive chemotherapy in combination with HART is an effective treatment for medulloblastoma in adults, and this approach seems to overcome previously-recognised risk factors.

Keywords: Medulloblastoma; Adults; Hyperfractionated accelerated radiotherapy; High-dose chemotherapy; Young adult cancer; Brain tumours

1. Introduction

Medulloblastoma is a malignant neuroectodermal tumour that is uncommon in adults. The median age at diagnosis in children is 5 years [1], while in adults there is no distinct peak and the progressively declining incidence seen in older children simply continues with advancing age. Medulloblastomas account for less than 3% of all adult primary central nervous system (CNS) neoplasms. In most reported series, the 5-year survival rate for adult medulloblastoma ranges roughly between 50% and 60%, regardless of risk category, while the 10-year survival rate falls to 40–50% [2–4]. Outcome has been improved in adults treated more recently, with 5-year survival rates up to 80% [5–7]. This may be due to better surgical, radiotherapeutic and imaging techniques and perioperative care.

The benchmark of therapy for adults with medulloblastoma is maximal feasible surgical resection followed by 35–36 Gy neuraxis radiotherapy plus a boost to the

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whole posterior fossa up to a total dose of 54–55 Gy. There is no consensus as to the real benefit of chemotherapy and analyses of responses to a given regimen are limited due to the wide variety of drugs and schedules employed, the small series homogeneously treated, and studies spanning lengthy periods of time [2,5,8,9].

On the other hand, the role of chemotherapy is well established in paediatric oncology. Prospective studies have shown that systemic chemotherapy may benefit children with high-risk medulloblastoma, even if the disease risk assignment has been refined over the years [10,11]. Moreover, chemotherapy is given to non-metastatic young patients to enable a lower dose of radiation, thereby reducing cognitive and growth effects without jeopardising survival given that reduced-dose neuraxis radiotherapy alone (23.4 Gy) has been found to be associated with an increased risk of relapse [12–14]. Such treatment applies only to patients over the age of 3–5 years. Younger children are treated with a 'baby protocol', which does not use whole central nervous system radiotherapy, but yields reduced survival rates.

We report here on our series of adults treated according to paediatric protocols, focusing on the potential role of intensive chemotherapy in combination with hyperfractionated accelerated radiotherapy (HART) in determining survival.

2. Patients and methods

2.1. Patients

This analysis considered 26 patients over 18 years old who had a medulloblastoma newly diagnosed between April 1987 and March 2003. The patients were divided into two homogeneously-treated chronological groups (group A, 1987–1996, $n = 12$; group B, 1997–2003, $n = 11$). Three additional cases received a tailored regimen. All patients were referred to the Istituto Nazionale Tumori (Paediatric Oncology Unit) or the Ospedale Niguarda Ca′ Granda in Milan for appraisal concerning adjuvant treatment. During the same period, 200 new cases of medulloblastoma in patients under 18 years old were registered at our institutions, thus representing a child-to-adult ratio of nearly 8:1.

Information was collected on preoperative physical examinations, radiology reports, detailed surgery reports, the type of postoperative treatment and follow-up evaluations. All patients underwent routine staging including magnetic resonance imaging (MRI) of the brain and lumbar puncture to assess cerebrospinal fluid (CSF) cytology. Spine MRI was performed in 19 patients (routine since 1997, while a myelogram was performed earlier). Systemic metastases were not sought at diagnosis, unless there were tell-tale symptoms. The extent of disease at diagnosis was described by the Chang staging system [15].

2.2. Treatment

2.2.1. Regimen A

In the 1987–1996 series (group A, $n = 12$), patients were assigned to either standard-risk or high-risk groups, and then given risk-adapted chemotherapy. The high-risk designation coincided with a residual tumour greater than 1.5 ml on postoperative radiology report, or evidence of metastases. Patients who did not fulfil these criteria were regarded as standard-risk. After surgery, standard-risk patients received three doses of weekly intrathecal methotrexate (MTX) 10 mg/m^2, two doses of weekly intravenous (i.v.) vincristine (VCR) 1.5 mg/m^2, radiotherapy as detailed below, and post-radiation maintenance with VCR (every 3 weeks) and lomustine (CCNU) orally 80 mg/m^2 (every 9 weeks) for 1 year. High-risk patients received the above treatment in addition to courses of i.v. MTX 8 g/m^2 on days 1, 8, 16 and 24, before radiotherapy [16].

2.2.2. Regimen B

Since 1997, patients were treated homogeneously regardless of initial tumour extent. Group B entered an up-front chemotherapy program, with the sequence of intensive-dose non-cross-resistant drugs given at the times shown in Fig. 1. Eleven patients received i.v. MTX 8 g/m^2 plus VCR following surgery, etoposide 2.4 g/m^2, cyclophosphamide 4 g/m^2 plus VCR, carboplatin 800 mg/m^2 plus VCR, and, following radiotherapy, 1-year VCR-CCNU maintenance. High-dose MTX was administered as a 6-h infusion with a 12-h i.v. alkaline prehydration and a 48-h posthydration, followed by leucovorin rescue starting 24 h after beginning MTX infusion, every 6 h for 12 doses of 15 mg each.

Granulocytes $\geqslant 1.0 \times 10^9$/l and platelets $\geqslant 100 \times 10^9$/l were required at the time scheduled for administering the drugs. Granulocyte colony-stimulating factor (G-CSF) was scheduled after etoposide and

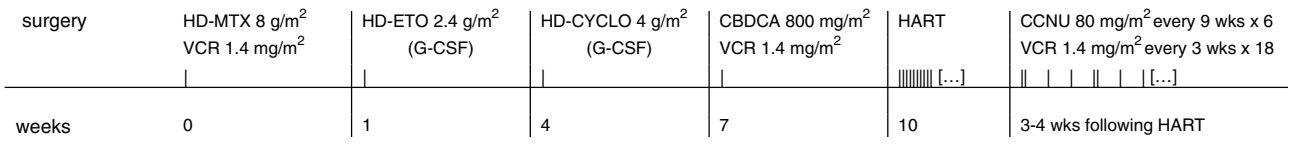

Fig. 1. Regimen B (1997 onwards). HD, high-dose; MTX, methotrexate; ETO, etoposide; CYCLO, cyclophosphamide; CBDCA, carboplatin; HART, hyperfractionated accelerated radiotherapy; VCR, vincristine; CCNU, lomustine.

cyclophosphamide, while G-CSF was recommended in the event of febrile neutropaenia following carboplatin administration.

Patients in group B who did not achieve a complete remission status before radiotherapy were scheduled to receive two myeloablative doses of thiotepa (900 mg/m^2) and autologous stem cell rescue as treatment intensification. That is why regimen B included peripheral blood stem cell collection by leukapheresis and cryopreservation following either etoposide or cyclophosphamide.

2.2.3. Radiotherapy

After the blood count recovered from initial chemotherapy, patients received craniospinal irradiation (CSI) followed by a posterior fossa boost. All patients were irradiated with a 6-MV linear accelerator at the Istituto Nazionale Tumori in Milan, with either conventional fractionation (regimen A) or a HART schedule (regimen B).

Patients in group A ($n = 12$) were conventionally irradiated with single 1.5–1.8 Gy fractions daily, 5 d a week, for a total dose of 36 Gy to the craniospinal axis and 55 Gy to the posterior fossa.

Since 1997, group B was administered HART, scheduled with two daily 1.3 Gy fractions 6 h apart, 5 d a week, for a total 15 d of treatment, reaching a dose of 39 Gy to the neuraxis, plus 1.5 Gy twice a day, for 7 treatment days, to give a boost of 21 Gy to the posterior fossa, thus delivering a total dose of 60 Gy to the posterior fossa. In the event of residual lesions within the posterior fossa or metastatic nodules, an additional boost of 9 Gy was delivered in 6 twice daily 1.5 Gy fractions. HART was started 3 weeks after administering carboplatin, or when granulocytes were $\geqslant 1.0 \times 10^9$/l and platelets were $\geqslant 75 \times 10^9$/l.

Two of the three patients given a tailored treatment had immediate conventionally-fractionated radiotherapy after surgery, then 12 months of VCR-CCNU. The third case received 4 monthly courses of cisplatin plus etoposide, then HART.

Informed consent was obtained from all patients. Both the studies were approved by the institutional ethical committee.

2.3. Statistics

Disease-free survival (DFS) is defined as the interval between surgery and disease progression or relapse. Overall survival (OS) is defined as the interval between surgery and death from any cause. Patients with no adverse events were censored at the latest follow-up. At the time of the study, no patient had been lost to follow-up. Actuarial curves were constructed by the Kaplan–Meier method [17]. Subgroup comparisons were drawn using the log-rank test [18].

3. Results

3.1. Patients

Patient characteristics are listed in Table 1. The median patient age was 26 years (range 18–41 years). There were 13 female and 13 male patients. The presenting symptoms included headache, nausea and vomiting in 57% of patients. Four patients were permanently shunted at initial surgery to relieve symptomatic hydrocephalus. Eight primary lesions were confined to midline structures, 16 were restricted to one cerebellar hemisphere or involved both midline and lateral structures (4 cases); 2 patients had a cerebellopontine angle tumour. In an attempt to remove as much tumour as possible from the posterior fossa without inducing neurological impairment, surgery involved gross total resection in 21 patients, and incomplete resection in 5. The desmoplastic variant was found in 6 cases, glial differentiation in 1; the remaining tumours exhibited classical histological features.

Eighteen patients had standard-risk disease, defined as less than 1.5 ml of residual tumour and no evidence of spread beyond the primary tumour (Chang M0). Eight patients had high-risk disease based on positive CSF cytology (M1, $n = 2$), multiple cerebellar metastases (M2, $n = 1$), spinal metastases (M3, $n = 4$) and greater than 1.5 ml of residual tumour ($n = 1$). Six high-risk cases were enrolled in regimen B study (M1 $n = 1$, M2 $n = 1$, M3 $n = 4$), one was among those who received regimen A (due to a residual tumour greater than 1.5 ml) and one was on a tailored therapy (M1). The low incidence of spinal metastases in group A may be related to myelogram (performed in 7 out of 12 patients) being less sensitive than spine MRI.

Two high-risk patients in group B received high-dose thiotepa intensification and autologous stem cell rescue before radiotherapy: these were a 21-year-old girl with residual malignant cells in the CSF before irradiation and a 34-year-old man with a residual cerebellar nodule at the end of initial chemotherapy.

For the series as a whole, chemotherapy was started a median 30 d (range 10–56 d) after surgery. The interval between surgery and radiotherapy ranged between 41 and 75 d (median 53) in regimen A, and between 106 and 141 d (median 118) in regimen B. Patients who received carboplatin (as scheduled in regimen B) were able to start radiotherapy within a median 29 d (range 24–35 d) after administration of the drug.

3.2. Regimen B-related toxicity

Eighty-two percent of patients had National Cancer Institute/Common Toxicity Criteria (NCI/CTC) grade 4 neutropaenia after etoposide administration, 73% after cyclophosphamide and 27% after carboplatin. The

Table 1
Patient characteristics

Patient	Age (years)	Year of diagnosis	Disease status post-surgery	Chang stage	Treatment regimen	OS (months)	Outcome
1	25	1988	ED	T2M0	A	22	DOD
2	41	1988	NED	T2M0	A	198+	CCR
3	18	1988	NED	T2M0	A	48	DOT
4	21	1992	NED	T2M0	A	150+	CCR
5	24	1990	NED	T2M0	A	69	DOD
6	29	1992	NED	T2M0	A	143+	CCR
7	21	1987	NED	T2M0	A	129	DOD
8	19	1991	NED	T2M0	A	55	DOD
9	19	1992	ED	T2M0	A	32	DOD
10	19	1987	NED	T3M0	A	209+	CCR
11	26	1988	NED	T2M0	A	200+	CCR
12	29	1987	NED	T2M0	A	30	DOD
13	19	1997	NED	T3M0	B	81+	3rd CR
14	38	2001	NED	T2M0	B	39+	CCR
15	41	2001	NED	T2M0	B	39+	CCR
16	28	2001	ED	T3M3	B	42+	CCR
17	32	2000	NED	T2M3	B	46+	CCR
18	22	1999	NED	T2M3	B	69+	CCR
19	21	2000	NED	T3M3	B	45+	CCR
20	30	2002	NED	T2M0	B	31+	CCR
21	34	2002	NED	T2M2	B	26+	CCR
22	27	2003	ED	T3M1	B	20+	CCR
23	20	2003	NED	T3M0	B	18+	CCR
24	30	1998	NED	T3M0	RT/VCR-CCNU	72+	CCR
25	30	1998	NED	T2M1	RT/VCR-CCNU	78+	CCR
26	30	2003	ED	T?M0	CDDP/ETO/HART	22+	CCR

NED, no evidence of disease; ED, evidence of disease; DOD, died of disease; DOT, died of toxicity (surgery-related death); CCR, continuous complete remission; CR, complete remission; CDDP, cisplatin; ETO, etoposide; RT, radiotherapy; OS, overall survival; HART, hyperfractionated accelerated radiotherapy; VCR, vincristine; CCNU, lomustine.

median duration of etoposide-related grade 4 neutropaenia was 3 d. Grade 4 thrombocytopaenia was recorded in 82% of cases after carboplatin, in 9% of cases after etoposide and never after cyclophosphamide. Febrile neutropaenic episodes occurred in 82% and 27% of patients after etoposide and cyclophosphamide, respectively, overall due to documented bacteraemia in 12% of cases. Packed red cells and platelets transfusions were given to 27% and 45% of patients, respectively. Transient mild elevation of liver transaminases was frequently recorded after high-dose MTX, though nadir values corresponding to NCI/CTC grade 3 were seen in only one patient. During maintenance minor protocol violation, such as a CCNU or VCR dose reduction, were necessary in two cases, because of persistent anorexia and grade 2 peripheral neuropathy, respectively.

In the two patients receiving high-dose thiotepa, neutrophil count $<0.5 \times 10^9$/l was observed from day +2 (both cases) to day +8 and +9 of marrow re-infusion, respectively, and a neutrophil engraftment (defined as a neutrophil count greater than 0.5×10^9/l for 3 consecutive days) at day +10 and +11. Platelet engraftment >25,000/mm^3 without transfusions occurred within 12 and 11 d of marrow re-infusion, respectively. The two patients were treated with antibiotics and antifungal agents for neutropaenic fever. Grade 4 oropharyngeal mucositis necessitated total parenteral nutrition for 11 d in one case. This same patient developed grade 4 transient neurotoxicity (generalised seizures, somnolence) on day +15 from the transplant, with a brain MRI showing a diffuse meningeal enhancement.

Ten patients concluded HART with no myelosuppression severe enough to prompt HART suspension. The remaining patient had a 2-d break due to symptoms of increased intracranial pressure and developed prolonged thrombocytopaenia requiring a suspension of the radiotherapy for 47 d before the posterior fossa boost. During radiotherapy, grade 3 thrombocytopaenia was recorded in 29% of the patients (none experienced grade 4), with a median time to the thrombocytopaenia nadir 21 d after beginning the HART. Grade 3 and 4 neutropaenia was recorded in 6% and 6% of patients, respectively, reaching a nadir 20 d (range 16–22 d) after beginning the HART.

3.3. Outcome

With a median follow-up of 46 months (range 18–209 months), 8 of the 26 patients have suffered a recurrence of medulloblastoma a median 34 months after the diagnosis (range 12–72 months) and 7 have died. Median survival following recurrence was 20 months (range

3–57 months). Failure occurred in 7 of the 12 patients in group A: 6 patients died of progressive disease, 1 during salvage surgery. Ten of the 11 patients in group B are alive and relapse-free after a median follow-up of 39 months (range 18–81 months). The one patient who experienced two consecutive isolated recurrences within the tumour bed (47 and 78 months after the diagnosis, respectively) is currently receiving salvage third-line chemotherapy following re-resection of the tumour. This patient had a standard-risk disease and was given chemotherapy and radiotherapy as prescribed by the protocol.

Patterns of recurrence showed that the posterior fossa was the most frequent site (75%), either alone ($n = 3$) or in combination with other CNS sites ($n = 3$). Bony metastases were detected in one relapsing patient. Five patients simultaneously developed tumour recurrence at multiple sites.

After a median observation time of 45 months (range 26–69 months), no signs of recurrence were recorded among the 5 patients in group B with Chang M2 or M3 disease. A 100% objective response rate was observed in this subgroup with measurable subarachnoid disease, with 3 complete remissions at the end of initial chemotherapy and 2 after HART.

The 3 patients who received a tailored regimen due to their impaired clinical conditions at diagnosis are alive and disease-free.

The 5-year Kaplan–Meier DFS and OS were $65 \pm 11\%$ and $73 \pm 10\%$, respectively, for the whole group (Fig. 2), and $50 \pm 14\%$ and $58 \pm 14\%$ for group A. At the time of this report, all patients of the group B are alive with no evidence of disease. Group B has been observed for a median of 39 months, yet the single failure occurred 47 months after diagnosis, thus raising concern that 6 patients are statistically at risk of recurrence. No risk factors could be evaluated in group B because only one failure occurred.

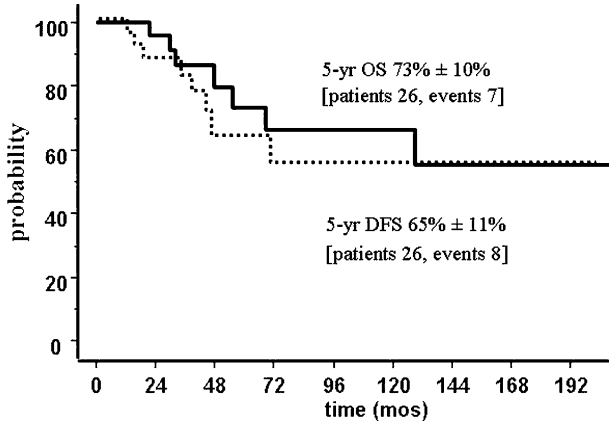

Fig. 2. Five-year survival rates for all patients. DFS, disease-free survival; OS, overall survival.

4. Discussion

Paediatric oncologists have reported that chemotherapy in addition to irradiation improved the outcome of children with high-risk [10,13,19], and standard-risk medulloblastoma [20]. The disease risk assignment has been refined over the years, now focusing on the presence of metastasis (M2/M3 Chang) as the real negative prognostic factor. In North America, a combined approach including both treatments has been increasingly accepted as standard practice in children, regardless of stage at diagnosis. Paediatric studies are more likely to address matters of neuraxis irradiation dose and schedule (conventional *versus* unconventional fractionation) and posterior fossa boost target volume, than whether or not to use adjuvant chemotherapy.

The traditional treatment for adults has consisted of surgery followed by craniospinal radiotherapy, plus a boost to the entire posterior fossa, with or without the addition of chemotherapy. Adult studies analysing the benefit of chemotherapy are discordant, mainly due to a paucity of controlled trials. Some authors found no difference in outcome between patients who did or did not receive chemotherapy [4,8,21], while others reported a significant survival improvement [2,3]. Other investigators support the role of drugs in preventing failure even in standard-risk adult patients, given the higher frequency of systemic spread in this age group [2,5,6].

Based on the assumption that the disease pattern is similar in adults and children, and that medulloblastoma is a chemosensitive as well as a radiosensitive disease, we have been homogeneously treating adults with medulloblastoma using paediatric protocols since 1987. The initial program that we investigated consisted of intrathecal or i.v. MTX plus VCR and conventional radiotherapy (regimen A). This program was changed in the mid-1990s in light of evidence of a potential benefit of an intensified chemotherapy regimen combined with HART (regimen B), as we observed in children.

One approach to improve the effect of chemotherapy on drug-sensitive tumours is to increase dose intensity. Good results have been obtained by doing so in children (and particularly in infants), achieving a durable remission and thus delaying radiotherapy until an older age, with consequently more limited cognitive sequelae [22,23]. High-dose chemotherapy has also been explored for relapsing adult medulloblastoma patients [24–26].

Group B received initial moderately intensive doses of sequential agents including MTX, etoposide, cyclophosphamide and carboplatin. One debatable point in regimen B was the timing of radiotherapy – a concern with pre-radiation high-dose chemotherapy is that the need to delay radiotherapy allows for potential tumour progression in the interim. The data from paediatric experiences are inconclusive on this point. The German HIT'91 randomised trial found a significantly lower

DFS in standard-risk children receiving pre-radiation sandwich chemotherapy than in those treated with immediate radiotherapy and maintenance (65% *versus* 78%, $P = 0.03$), but this difference was not seen in high-risk patients; moreover, sandwich and maintenance chemotherapy regimens were different [27]. On the other hand, good results were obtained with intensive pre-radiation chemotherapy in low-stage medulloblastoma, reaching a 5-year DFS of 74% [28], and by the Pediatric Oncology Group #9031 study, recording a 78% 2-year DFS in high-stage children, albeit with higher doses of radiation (40 Gy) [29]. In our series none of the tumours progressed during chemotherapy or radiotherapy. Using the chemo-radiotherapy sequence, the delivery of drugs to the tumour bed might be expected to be maximal. The combination sequence avoids irradiation-induced bone marrow suppression, which can limit drug delivery and dose intensity if chemotherapy is given after irradiation. We also found that the designed sequence did not affect the dosage and timing of radiotherapy, so it did not jeopardise radiation dose intensity. Group B was able to start radiotherapy within a median 118 d (range 106–141 d) after surgery (*versus* 84–91 d as planned). No significant regimen B-related acute morbidity was recorded, other than myelosuppression. This is worth noting if we bear in mind that there is evidence of chemotherapy being less well tolerated in adolescents and young adults than in children [9,30].

Group B has been observed for a median of 39 months, yet the only failure so far occurred 47 months after diagnosis. This long latency before recurrence raises concern that additional late failures may occur. An extended follow-up may consequently be necessary to confirm these data. On the other hand, the 5 patients with Chang M2–M3 disease treated with chemotherapy plus HART as designed in regimen B are recurrence-free. In children, the presence of metastases is of major prognostic significance [7]. The encouraging results we have obtained in high-risk adult patients treated according to regimen B were superimposable on our institutional paediatric series. The updated results of the same intensive dose chemotherapy plus HART treatment in 28 children with metastatic medulloblastoma (9, 4, 14 and 1 of the patients had M1, M2, M3 and M4 Chang stage disease, respectively) treated at our institution between 1997 and 2003 documented actuarial 4-year DFS and OS of 77% and 84%, respectively (with a median follow-up of 47 months) [31].

Overall, the posterior fossa was the most frequent site of failure in the present adult series, despite radiation doses $\geqslant 55$ Gy. HART was used to increase the total radiation doses, thus improving the chances of local disease control, while reducing the total treatment time (given a higher radiotherapy dose intensity). There has been only one case of isolated failure within the tumour bed in group B, but an extended follow-up is needed to strengthen the hypothesis that HART could improve the chances of local tumour control.

Some investigators have documented some degree of cognitive deficit in young adults treated for medulloblastoma [32]. However, the cognitive outcome in the children aged 10–18 years treated for medulloblastoma according to the same regimen A was remarkably good, and virtually indistinguishable from control subjects [33]. The more recently treated group B is being prospectively followed up for late endocrinological deficits. The group is undergoing neuropsychological tests based on evidence of psychological and social recovery problems among our more recently treated adolescents with medulloblastoma [34].

In conclusion, sequential, moderately intensive chemotherapy followed by HART seems to overcome previously recognised risk factors, such as metastasis at presentation. These results are interesting, but far from definitive and should be tested in a larger series of patients. It appears from this study that the delay of radiotherapy does not result in a worse outcome, provided that the chemotherapy regimen is sufficiently intensive and effective. Moreover, the relative role of chemotherapy *versus* HART in obtaining these results should be clarified.

We emphasise that young adults with medulloblastoma should be contacted for recruitment in clinical trials, at paediatric units or in dedicated neuro-oncology programs, to improve new data acquisition relevant to this age group. It is important to add that a neuropsychological and neuroendocrine sequelae follow-up is also warranted in adults.

Conflict of interest statement

None declared.

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