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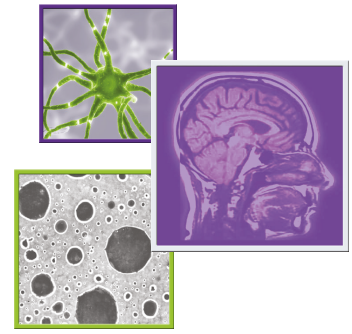

Postradiation platinum–etoposide in adult medulloblastomas: retrospective analysis of hematological toxicity

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Aim: Adult medulloblastomas (MB) are rare, and optimal post-craniospinal irradiation (CSI) chemotherapy is not yet defined. We investigated hematological toxicity in patients treated with platinum–etoposide (EP) post-CSI. **Methods:** Retrospective, single-institution study to determine hematological toxicity in adult MB patients treated with EP (1995–2022). **Results:** Thirteen patients with a median follow-up of 50 months (range, 10–233) were analyzed. Four discontinued treatment due to toxicity, one after 1, 3 after 3 cycles. Hematological toxicities included grade 3 (5 patients) and grade 4 (6 patients). Two patients experienced post-treatment progression and died 16 and 37 months from diagnosis. **Conclusion:** Post-CSI EP demonstrates acceptable hematological toxicity in adult MB. However, the small cohort precludes definitive survival outcome conclusions. Prospective studies for comprehensive comparisons with other regimens are needed in this context.

Plain language summary: Our study aimed to understand the effect of a chemotherapy combination (platinum and etoposide) on blood counts in adult patients with medulloblastoma after craniospinal radiation. Medulloblastoma is a rare brain cancer in adults. We analyzed data from 13 adult patients with medulloblastoma. The results show that the treatment leads to significant blood count-related side effects. Four of the patients discontinued their treatment early. Blood counts improved again after completion of treatment. Two patients had the tumor grow back after treatment and died later. Overall, the effect from this chemotherapy combination on blood counts was felt to be acceptable. The number of patients in this study was small, and more research is needed to determine the overall effectiveness of this treatment.

Tweetable abstract: Retrospective analysis shows acceptable hematological toxicity of post-CSI platinum–etoposide in adult medulloblastoma. #medulloblastoma #chemotherapy

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Keywords: adult medulloblastoma • cisplatin • craniospinal radiation • etoposide • medulloblastoma

Selecting the appropriate treatment for adult patients with newly diagnosed medulloblastoma (MB) is challenging. While MB is one of the most common cancers in children, it is a rare type of brain tumor in adults. In the USA, there are only about 150 diagnoses of adult MB annually [1]. There have been no randomized clinical trials dedicated to this patient population to guide the optimal choice of chemotherapy.

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Adult MB treatment standards have changed over time, with maximal safe surgical resection a universally desirable goal, followed by craniospinal radiation (CSI). However, only until recently has the role of adjuvant chemotherapy been controversial [2]. This is because adult MB patients could receive higher doses of craniospinal radiation compared with pediatrics due to absence of developmental toxicities, while simultaneously suffering more hematological adverse effects. Differences in hematological toxicity between proton and photon CSI, favoring proton CSI, have been described; however, data on adult patients have remained limited [3,4]. Adjuvant chemotherapy was not an automatically accepted standard until the past few years, with institutions making individual chemotherapy decisions based on clinical factors such as extent of resection, patient functional status, hematological toxicity and reserve evaluations after the completion of radiation. Frequently, adults require dose modifications and early discontinuation of the treatment due to toxicity, particularly when older than 45 years of age [5]. Based on an accumulation of retrospective data with a heterogeneous adult MB population and treatment regimens, adjuvant chemotherapy is now an accepted standard of care in all adult MB patients with appropriate blood counts after the completion of radiation [6,7]. However, there is no single recommended chemotherapy regimen used for adult MB as data are derived from the pediatric literature and have little prospective support in adult MB. Among the most commonly used combinations are a platinum agent, typically cisplatin or carboplatin, an alkylating agent, typically lomustine or cyclophosphamide and vincristine, referred to as the 'Packer Regimen', as well as vincristine, etoposide and carboplatin alternating with cyclophosphamide, referred to as the 'Taylor Regimen' [8–10]. The choice of either regimen typically is based less on established evidence in adult MB patients and more on provider familiarity with the regimen and perceptions of relative hematological toxicities.

Given concerns of toxicity and lack of guiding data in adult MB, other regimens have been used, including platinum and etoposide (EP) [11,12]. The rationale being that use of a two-drug regimen may pose less toxicity and may allow for more cycles. EP is similar to the Taylor Regimen but without the use of vincristine and cyclophosphamide. A rationale for omitting vincristine are concerns about neurotoxicity (peripheral neuropathy), drug delivery across the blood–brain barrier, and there are data to suggest that omitting vincristine does not negatively impact outcome [13].

EP is the standard first-line chemotherapy for patients with extensive stage small-cell lung cancer (SCLC), as well as other small cell cancers [10,14]. Oncologists are familiar in using this regimen with well-studied toxicity in cancer patients; however, data on toxicity of EP after CSI in adults are scarce. An Italian study described the toxicity in adult MB patients treated with a similar postradiation chemotherapy regimen, which included cisplatin (25 mg/m^2 on days 1–4) plus etoposide (40 mg/m^2 on days 1–4) or carboplatin (300 mg/m^2 on day 1) plus etoposide (60 mg/m^2 on days 1–3) [11]. Among patients that received this regimen (n = 24), the reported grade $\geq$3 adverse events included six cases of grade 3 neutropenia (25%), three cases of grade 4 neutropenia (13%) and one case of grade 3 thrombocytopenia (4%). While the aforementioned study provided other valuable insights, it did not extensively cover toxicity outcomes. There are no additional reports of toxicity with EP in MB after CSI.

To address the existing gap in the literature, our report aims to present our institutional experience using the EP regimen in adult MB patients, with a specific focus on evaluating the safety and tolerability of this treatment approach.

Materials & methods

This was a retrospective, single institution study on adult patients (age $\geq$18 years) with MB who were treated with EP chemotherapy after completion of CSI. The study was approved by the Johns Hopkins Medical Institutional Review Board (IRB00270580). To capture all adult MB patients treated with EP at our institution, we started a broad search of our cancer center registry. We screened all adult patients with the diagnosis of MB. We then narrowed our search to eligible patients who received treatment at our institution with CSI and EP. A full set of laboratory data and at least 1 month of follow-up after completion of the chemotherapy were required to assess for hematological toxicity. Patients' charts were reviewed independently by two authors for data accuracy.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 was used to classify hematologic toxicity. White blood cell decrease was classified as Grade 1 (lower limit of normal [LLN] to 3000/mm^3), Grade 2 (<3000 to 2000/mm^3), Grade 3 (<2000 to 1000/mm^3) or Grade 4 (<1000/mm^3). Absolute neutrophil count decrease was classified as Grade 1 (<LLN to 1500/mm^3), Grade 2 (<1500 to 1000/mm^3), Grade 3 (<1000 to 500/mm^3) or Grade 4 (<500/mm^3). Platelet count decrease was classified as Grade 1 (<LLN to 75,000/mm^3), Grade 2 (<75,000 to 50,000/mm^3), Grade 3 (<50,000 to 25,000/mm^3) and Grade 4 (<25,000/mm^3).

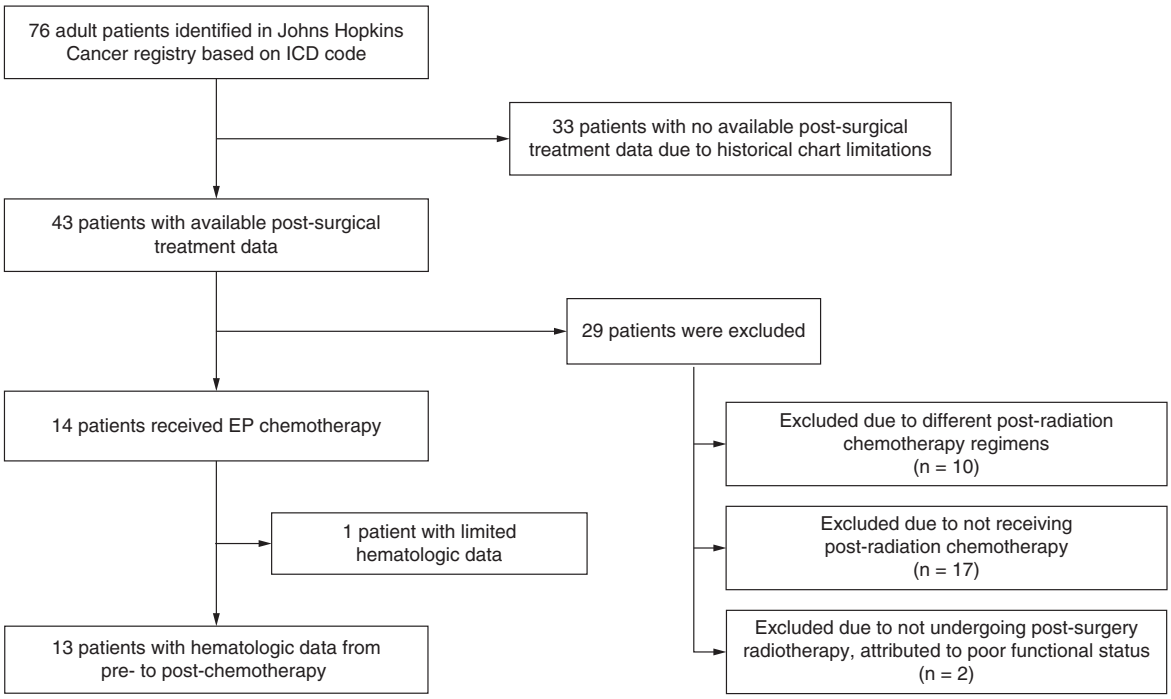

Figure 1. Flow diagram: identification of patients eligible for this analysis.
EP: Platinum–etoposide; ICD: International Classification of Diseases; N: Number.

A chart review of non-hematological toxicities was attempted; however, as symptoms were not systematically recorded and as completeness of adjunct reports (e.g., audiology notes) could not be assured, we decided to focus our report primarily on hematological data as blood counts reflect an objective measure of toxicity.

Statistical considerations

The choice of study methodology was based on a rare disease as a retrospective medical chart review. Prespecified inclusion and exclusion criteria of the study were the record selection method. The data were abstracted using prespecified data fields on medical diagnosis, treatments and outcomes of interest with no imputation for missing. Data analysis was descriptive, and data were presented with standard summaries. Some summary results have high variability due to small sample size.

Results

Patient characteristics

The initial search identified 76 adult patients with MB within our cancer center registry who were seen at our institute between 1995 and 2022 (Figure 1). Of these, 33 patients could not be included in the analysis due to incomplete postsurgical treatment data, primarily attributed to historical chart limitations. An additional 29 patients were excluded from the cohort as they did not meet the eligibility criteria for inclusion. Of the total patient cohort, 14 received EP chemotherapy after CSI and met the eligibility requirements for this analysis. One patient was subsequently excluded due to limited hematologic data, leading to a final cohort of 13 patients that met eligibility requirements for this analysis. Of the 13 patients, 10 (77%) were males (Table 1). Median age was 33 years (range, 22–47) at the time of diagnosis. All patients had a histological diagnosis of MB based on the WHO classification at the time of their tumor diagnosis. Chart review and/or retrospective data analysis stratified 8 of the 13 patients into the high-risk adult MB group (due to positive cerebrospinal fluid analysis, or metastatic disease or residual tumor >1.5 cm) (Table 2).

All patients underwent surgery for maximal safe tumor resection. Within a median of 46 days (range, 18–81) postsurgery, all patients started radiation treatment. All 13 patients completed craniospinal radiation, 8 with photon and 5 with proton therapy, and all patients received full dose (not reduced dose) radiation. Chemotherapy started within a median of 154 days (range, 89–274) after surgery (Table 2).

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Table 1. Patient demographics.

		Total number = 13
Sex	Females	3 (23%)
	Males	10 (77%)
Race	Asian	1 (8%)
	Black	6 (46%)
	White	6 (46%)
Age at diagnosis in years	Range	22–47
	Median	33

Chemotherapy tolerability

All 13 patients received at least one cycle of EP (Table 2). The median number of cycles was 4 (range, 1–6). One patient agreed to undergo only two cycles of treatment (patient #6) at the time of chemotherapy discussion. 69% of patients were able to complete the planned number of cycles. The initial dose of cisplatin was 60 mg/m^2 on cycle 1, day 1. The initial dose of etoposide was either 60 or 120 mg/m^2 in cycle 1, day 1 to cycle 1, day 3 or 5, respectively. Dose reduction was required for two patients. Among all 12 patients with available blood-count data post-radiation, most patients had normal WBC (67%), two patients (17%) had grade 1, two patients (17%) grade 1 leukopenia; only one patient (8%) experienced neutropenia (grade 2), All but one patient had normal platelet counts prior to start of chemotherapy (83%). During chemotherapy, five patients (42%) developed grade 3, and six (50%) grade 4 neutropenia. Compared with neutropenia, thrombocytopenia was less frequently observed and less severe. Three patients (25%) developed grade 1 and two (8%) grade 2 thrombocytopenia (Figure 2A). Overall, patients' blood counts showed improvement after the completion of treatment, with most returning to the normal range or improving compared with the nadir phase during chemotherapy. We analyzed the potential differential effect of proton versus photon CSI on post-CSI blood counts (Figure 2B, C & Supplementary Data). Patient numbers for each cohort were too small to draw firm conclusions from our dataset on a total of 13 patients. In addition, we analyzed whether there was a relationship between the number of chemotherapy cycles administered and hematological toxicity. The correlation coefficient of the severity of hematological toxicity and chemotherapy cycles was 0.08 (95% CI: -0.55–0.65; p = 0.82) based on the information available among the 11 patients in this study that had compete toxicity data for WBC, ANC and platelet count. The observed toxicities seem unlikely correlated with the number of chemotherapy cycles in this small dataset.

Survival

Patients were followed for a median of 50 months from diagnosis (range, 10–233; Table 2). Two of the 13 patients had progression within 11 months after three cycles of EP and 22 months after four cycles of EP and died due to progression of MB at 16 months and 37 months after original diagnosis, respectively.

Discussion

While evidence-based treatment recommendations and guidelines are available for the management of childhood MB, the optimal systemic therapy for newly diagnosed adult patients with MB is more controversial [2,6,7,11,12]. Traditionally, adjuvant chemotherapy is offered to adult patients with high-risk disease. However, compared with children, adult patients experience higher rates of toxicity, thereby limiting the doses and number of cycles of chemotherapy that can be administered. Given the differential toxicity signature of polychemotherapy in the post-CSI setting between children and adults, it is necessary to consider systematic de-escalation of existing regimens in the adult population that will allow for meaningful administration of chemotherapy after CSI while maintaining treatment efficacy and improving symptom burden as well as quality of life. To date, the only published data have been on single-arm prospective studies on different cisplatin-based chemotherapy regimens [15–17]. Especially the use of vincristine has been questioned in adults with MB. While vincristine is used as part of standard regimens in children, this treatment is poorly tolerated in adults, mainly due to development of sensorimotor and autonomic neuropathy that frequently leads to early termination of this drug. In addition, data in rats with gliosarcoma treated with intraarterial vincristine, demonstrated negligible penetration of normal rat brain and tumor, challenging the role of vincristine for treatment of primary cancers of the CNS [13].

Table 2. Clinical characteristics, treatment and outcome of patients with adult medulloblastoma treated with cisplatin and etoposide.

Patient number (study ID)	Diagnosis (histological subtype)	Molecular subgroup	Age at diagnosis (year)	Sex	Race	Risk stratification	Type of CSI	CSI total dose (Gy)	CSI fractions	Chemotherapy dose and schedule (planned)	Number of cycles/planned	Outcome	Time to last follow-up (month)†
1	Classic MB	SHH-activated, TP53-wild-type	32	M	White	ND	Proton	54	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m2 d.1-3	4/4	Alive	50
2	Desmoplastic/nodular MB	ND	29	M	Black	ND	Photon	54	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	4/4	Alive	74
3	Classic MB	SHH-activated	36	M	Black	High	Photon	57.6	32	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	6/6	Alive	91
4	Classic MB	ND	43	M	White	High	Photon	54	30	Cis at 60 mg/m^2 d.1 Eto at 60 mg/m^2 d.1-5	4/4	Alive	148
5	Classic MB	ND	26	F	Black	ND	Photon	55.8	31	Cis at 60 mg/m^2 d.1 Eto at 60 mg/m^2 d.1-5	3/4	Deceased	16
6	Large cell/anaplastic MB	ND	33	M	White	High (+CSF)	Photon	54	30	Cis at 60 mg/m^2 d.1 Eto at 60 mg/m^2 d.1-5	2/2	Alive	171
7	Classic MB	ND	24	M	White	High (+CSF)	Photon	54	30	Cis, Eto‡	6/6	Alive	233
8	Classic MB	SHH-activated	44	F	Black	High (LMM)	Photon	55.8	31	Cis at 60 mg/m^2 d.1 Eto at 60 mg/m^2 d.1-3	4/4	Deceased	37
9	Classic MB	Non-Wnt/non-SHH (group 4)	25	F	White	High (+CSF)	Proton	54	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	1/4	Alive	56
10	Large cell/anaplastic MB	SHH-activated, TP53-wild-type	47	M	Black	ND	Proton	49.2	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	6/6	Alive	26
11	Classic MB	SHH-activated, TP53-wild-type	46	M	Asian	ND	Photon	54	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	3/6	Alive	20
12	Large cell/anaplastic MB	SHH-activated, TP53-wild-type	22	M	Black	High	Proton	52.4	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	4/4	Alive	10
13	Desmoplastic/nodular MB	SHH-activated	33	M	White	High	Proton	54	30	Cis at 60 mg/m^2 d.1 Eto at 120 mg/m^2 d.1-3	3/4	Alive	14

†Until last contact or till date of death.
‡Dose and schedule information not available.
+CSF: Cerebrospinal fluid positive for cancer cell; Cis: Cisplatin; CSI: Craniospinal irradiation; d.: Day; Eto: Etoposide; F: Female; LMM: Leptomeningeal metastasis: M: Male; MB: Medulloblastoma; ND: No data.

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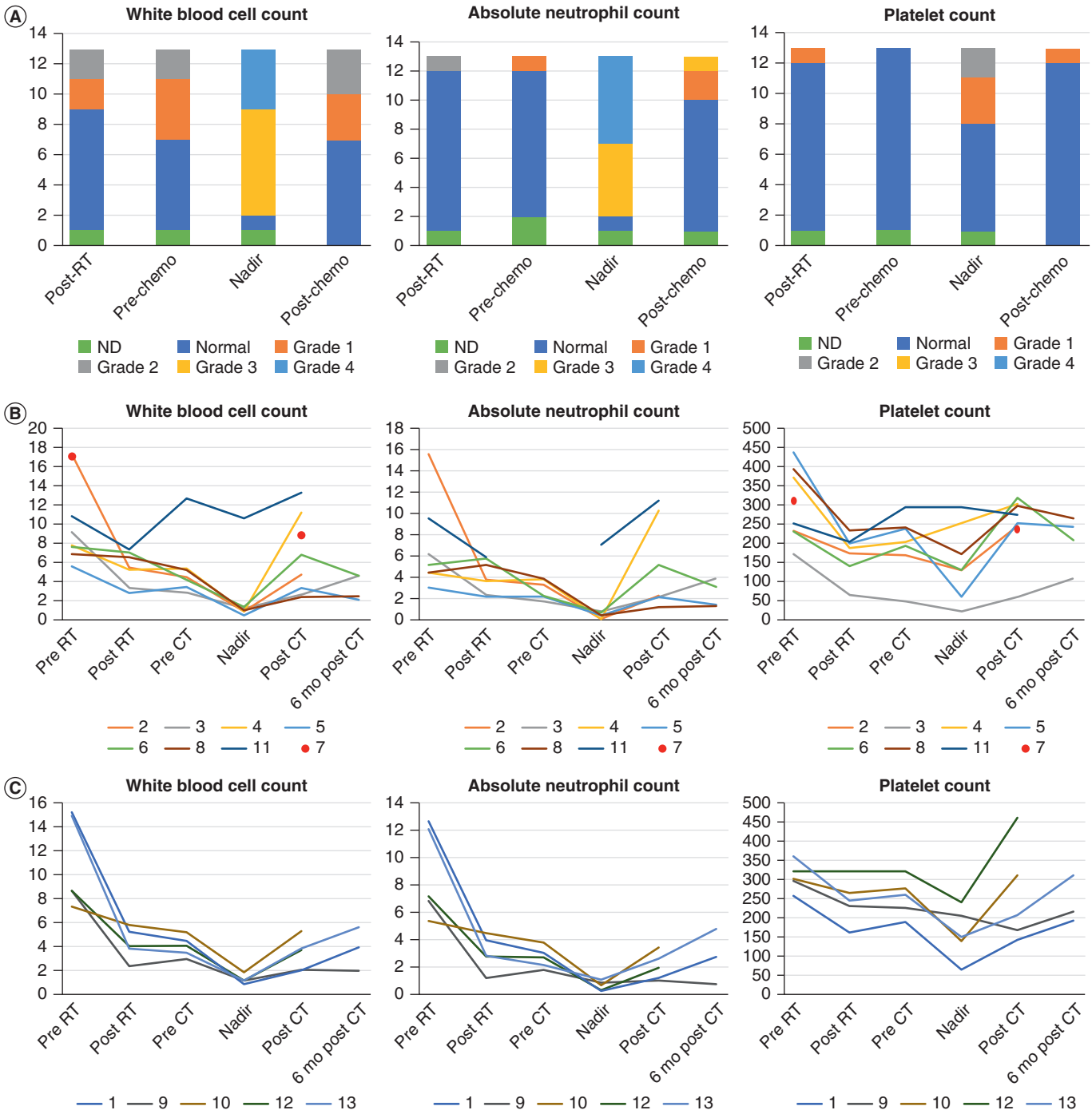

Figure 2. Illustration of hematological toxicity. (A) Comparison of CTCAE grading of white blood cell counts, absolute neutrophil counts, and platelet counts post-craniospinal irradiation (CSI), prechemotherapy, at the count nadir and post-chemotherapy (data of photon and proton radiation therapy patients combined). **(B)** Blood counts during treatment over time for photon radiation therapy patients. **(C)** Blood counts during treatment over time for proton radiation therapy patients. Each line and color represents one individual patient. ND: No hematological data for this time point.

In this report, we summarized our institutional experience with platinum and etoposide (EP) in the treatment of adult MB. Patients were offered adjuvant chemotherapy after CSI, based on their performance status and blood counts. We found that EP showed noticeable but acceptable hematological toxicity profile, which compares favorably to other polychemotherapy regimens available based on the pediatric regimens and limited prospective

data in adults. It is of note that all patients in this patient cohort received full dose CSI, as it was the current standard guideline-supported approach for adult patients at time of treatment at our institution. The question of whether to offer patients with standard risk adjuvant chemotherapy was discussed as there are no conclusive data in the literature of adult MB for the addition of chemotherapy to full dose CSI in this setting. The cohort of patients presented in this study includes only the patients that received adjuvant chemotherapy. The question of offering reduced dose CSI plus chemotherapy for standard risk adult patients has been revisited by an Italian and French study, showing no significant difference in 5-year PFS and OS between adults and children treated with reduced dose RT and chemotherapy [18]. These data suggest that reduced dose CSI plus chemotherapy should be reconsidered in adult patients with standard risk MB.

Platinum and etoposide combination therapy is a well-established regimen with known side-effect profile and long-term toxicity data that has been used for small cell cancers, including SCLC and germ cell tumors. While there are no significant differences in survival in SCLC between cisplatin-etoposide and carboplatin-etoposide, their side-effect profiles do vary. Although cisplatin is associated with less myelosuppression than carboplatin, it is associated with severe ototoxicity as well as nephrotoxicity, whereas carboplatin is more myelosuppressive [19]. There are currently no data on differential efficacy of cisplatin versus carboplatin for the treatment of primary cancers of the CNS as trials in MB primarily used cisplatin-based regimens. Based on this, and as myelosuppression is the chemotherapy-limiting toxicity observed in MB after CSI, one may favor cisplatin and etoposide over carboplatin and etoposide, using a standard SCLC protocol. Appropriate renal function is necessary if cisplatin is chosen as the regimen for an adult patient with MB.

This report has several significant limitations, including the retrospective nature of this report and the small sample size. Data on non-hematological toxicity, including audiology data, were not uniformly reported in the available retrospective charts, which is why this report is primarily focused only on hematological toxicity. It is noted that in future prospective studies, non-hematological toxicity and especially audiology data needs to be captured to assess the full scope of treatment-related adverse effects. In addition, most patients in this historical cohort received photon CSI, and proton therapy has been found to be associated with less toxicity, including hematological toxicity compared with photon therapy. Our dataset was too small to assess the differential impact on photon versus proton CSI in the patient cohort studied. To accurately describe hematological toxicity post-CSI, we limited our final dataset only to adult patients treated at our institution and for whom comprehensive blood work was available. Although all patients in this cohort had high-risk features of their disease, there is significant heterogeneity regarding MB biology between the patients. In addition, patients received different regimens between the years they were treated. Nonetheless, in current clinical practice, most adults with any subtype of high-risk MB are offered CSI followed by chemotherapy although CSI alone is considered an option for adult patients with standard risk MB [10]. At present, targeted therapy is typically reserved for the recurrent setting for certain subtypes of MB within a clinical trial. For example, sonidegib or vismodegib, SHH pathway inhibitors, show promising results in the treatment of SHH subtype MB that need to be further evaluated in the clinical setting [20]. It is expected that the more we learn about the biology of the heterogenous group of MBs, the more targeted treatment options will be discovered and available for clinical use. In the meantime, traditional cytotoxic drugs continue to be the mainstem of MB treatment along with CSI.

Based on the overall favorable toxicity we experienced with EP and the descriptive data on outcome in this small dataset, we feel that further prospective study of this regimen would be justified. Ideally, this would be in the form of a prospective study on adult patients with newly diagnosed MB, comparing EP to one of the existing polychemotherapy regimens. However, studying the efficacy of systemic therapies in newly diagnosed adult MB is challenging due to its rarity in this population, as well as due to the long time necessary to reach survival end points. Thus, similarly to other rare cancers, such a trial would require a multi-center effort with the possible involvement of consortia. In addition to studying efficacy of this regimen in the adjuvant setting in newly diagnosed adult MB, it would be reasonable to also study this regimen in recurrent adult MB, especially in patients that did not receive etoposide as part of their initial regimen. Nevertheless, MB is one of the primary brain cancers in which the addition of systemic therapy can yield meaningful improvement in long-term survival. As a prospective trial would be very challenging to conduct due to the rarity of this disease in adults, there would also be value of prospectively capturing real-life treatment data within institutional or collaborative patient registries. Whether within a prospective trial or within carefully procured registries, the differential effect of proton versus photon therapy should be considered, as data have shown less toxicity with proton therapy in the post-CSI setting. A coordinated effort to prospectively

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compare the different regimens and to optimize treatment options for this disease would likely be of great benefit to our patients.

Conclusion

Data on the optimal choice post-CSI chemotherapy in adult MB are lacking. Myelosuppression after CSI is a special challenge in these patients, and as a result, there is a need to define less aggressive chemotherapy options for this patient population. The hematological toxicity of EP in this retrospective patient cohort was significant but reversible. Prospective data are needed to define the efficacy of EP in this patient population, and to compare toxicity with that of other regimens used in this rare disease. However, it is unlikely that such a study is feasible in adults due to the rarity of MB in this patient population.

Summary points

- Conclusive and prospective data on chemotherapy after craniospinal irradiation (CSI) in adult medulloblastomas are lacking.
- As post-CSI myelosuppression significantly limits the amount of cytotoxic therapy that can be given in these patients, there is a need to define safety and efficacy of less intense regimens in this clinical setting.
- This small, retrospective study on 13 patients that received post-CSI in adult medulloblastoma shows significant but reversible hematological toxicity.
- Further study is needed to compare toxicity and efficacy of platinum–etoposide with other existing regimens; however, prospective studies will be extremely difficult to conduct due to the rarity of medulloblastomas in adults.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cns-2023-0029

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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