Efficacy of Intrathecal Methotrexate in Children with High-risk Medulloblastoma over 3 years: A retrospective study from a single center

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Abstract

Background To evaluate the therapeutic benefits and side effects (especially leukoencephalopathy) of intrathecal methotrexate (MTX) in children aged over three years old with high-risk medulloblastoma (MB). **Methods** In the present retrospective study, patients who received intrathecal MTX during chemotherapy were classified as MTX group, while those receiving cerebrospinal fluid (CSF) cytology analysis only were recruited in control group. **Results** Among the 46 MB patients, 32 were classified in MTX group, whereas 14 in control group. For those 32 patients in MTX group, 27 (84.38%) had metastatic disease, 3 (9.38%) had diffuse anaplasia, and 3 (9.38%) had residual disease greater than 1.5 cm ^{2}. Molecular subgroup classification was available in 28 (87.5%) patients. Of those 14 patients in control group, 8 (57.14%) had metastatic disease, 3 (27.27%) had diffuse anaplasia, and 6 (42.86%) had residual disease greater than 1.5 cm ^{2}. Molecular subgroup classification was available in 6 (42.86%) patients. The 5-year progression-free survival (PFS) was 70.99% (95% CI, 58.22%-90.42%) and 5-year overall survival (OS) was 72.99% (95% CI, 60.41%-93.06%) for MTX group, while those were 41.67% (95% CI, 17.93%-66.92%) and 50% (95% CI, 27.88%-77.14%) for control group, separately. Among the 32 patients in MTX group, 6 (18.75%) with group 4 disease developed MTX-related acute leukoencephalopathy and one of them died. **Conclusions** Intrathecal MTX improves the 5-year PFS and OS for children with high-risk MB. However, intrathecal MTX is not recommended for patients with group 4 MB due to the high risk of acute leukoencephalopathy.

Introduction

Medulloblastoma (MB) is one of the most common malignant brain tumors in children[1]. Approximately one-third of children present with a high risk of disease at the time of diagnosis. The survival of these patients remains unfavorable, and the 5-year progression-free survival (PFS) rate is >60% in the last few years by different strategies[2]. Most recently, a clinical trial shows that for children aged over 5 years with high-risk MB, the 5-year PFS is 76% after high-dose chemotherapy with stem cell support followed by conventional craniospinal radiation therapy and maintenance treatment [3]. The survival rate obtained in this trial is in the upper range of the recently obtained encouraging results from different studies[2, 4]. In contrast to standard-risk MB, there is no gold standard treatment for high-risk MB. Even though, it seems that treatment based on high-dose chemotherapy and conventional radiotherapy can result in a high survival rate in children with newly diagnosed high-risk MB.

In our institution, autologous stem-cell transplantation is not routinely performed due to its high cost. In addition, it also brings a burden on 6-14% of patients who are associated with death[5]. In view of this, methotrexate (MTX) intrathecal injections were adopted for high risk MB. Due to the relative lack of data concerning the efficacy and toxicity of MTX intrathecal injections in central nervous system (CNS) embryonal tumors, it remains controversial about whether MTX intracranial injection should be administered. MTX has been used in European trials, but it is rarely adopted in the United States because of the association with

radiation-induced leukoencephalopathy. To the best of our knowledge, there is no previous study reporting acute leukoencephalopathy induced by MTX treatment for MB during chemotherapy.

Here, a retrospective study was conducted to evaluate the therapeutic benefits of intrathecal MTX in children aged over three years with high-risk MB, so as to objectively evaluate the intervention and side effects, especially leukoencephalopathy for children with high risk MB.

Methods

Patients

This study was approved by the Ethical Institution of our hospital. Medical records from patients aged over 3 years with high-risk MB between January 1st, 2010 and December 31st, 2018, were reviewed. High-risk MB was defined as residual disease >1.5 cm^2, diffuse anaplasia histology and metastatic spread of disease (M0,1,2,3) according to the Chang's classification[6]. Patients receiving intrathecal MTX were classified into MTX group, while those without intrathecal MTX into control group. Patients in WNT subgroup were excluded due to the good previous treatment response.

The following data were extracted from each patient, including age, gender, histological subtype, tumor stage, risk group, molecular subgroup, chemotherapy regimen and dosage, details of MTX intracranial injection, clinical manifestation of leukoencephalopathy, treatment regimen of leukoencephalopathy, and patient outcomes (including the cause of death). Data collection from clinical records of patients was approved by the Institutional Review Boards. All data were anonymous, and informed consent was waived due to the retrospective observational nature of this study. Additionally, written informed consents were obtained from the parents or legal guardians of patients before the initiation of chemotherapy.

Statistical analysis

PFS and overall survival (OS) were estimated by the Kaplan-Meier method with Rothman's 95% confidence interval (CI). Meanwhile, median follow-up was estimated by the reverse Kaplan-Meier method. Hazard ratios (HR) and 95% CIs of multivariate Cox proportional hazard models were used to explore the effects of MTX intrathecal injection. Nonparametric data were compared by Mann-Whitney U test. The statistical significance level was set at $p < 0.05$. GraphPad Prism 9.4 was employed for all statistical and image analyses.

Results

Patients

From January 1st, 2010 to December 31st, 2018, a total of 46 patients aged over 3 years were diagnosed with high risk MB. The median age at diagnosis was 10.6 (range, 5-21) years. There were 33 male and 13 female patients. For biological analyses, 34 (73.9%) of the 46 MB patients were included in molecular analyses. In total, 32 patients received intrathecal MTX and were classified in MTX group, whereas the remaining 14 were treated without intrathecal MTX and were in control group. For the 32 patients in MTX group, 27 (84.38%) had metastatic disease, 3 (9.38%) had diffuse anaplasia, and 3 (9.38%) had residual disease greater than 1.5 cm^2. Molecular subgroup classification was available in 28 (87.5%) patients, which assigned patients to WNT (n=0), SHH (n=5), group 3 (n=6), and group 4 (n=17) subgroups.

Among the 14 patients in control group, 8 (57.14%) had metastatic disease, 3 (27.27%) had diffuse anaplasia, and 6 (42.86%) had residual disease greater than 1.5 cm^2. Molecular subgroup classification was available in 6 (42.86%) patients, assigning patients to WNT (n=0), SHH (n=2), group 3 (n=1), and group 4 (n=3) subgroups.

The details of these patients are presented in Supplementary Table 1.

Treatments

All patients received initial maximum safe surgical tumor resection, and then 36 Gy craniospinal radiotherapy with boost to the posterior fossa at the 55.8 Gy cumulative dose with conventional fractionation at 1.8 Gy/d. Radiotherapy was initiated within 31 days after diagnostic surgery for all patients.

There were 9 patients in MTX group refusing chemotherapy after the completion of radiotherapy according to their parents' willingness. All of these patients developed relapsed disease 6 to 12 months after radiotherapy. Therefore, a second surgery was performed for the relapsed disease, and all of them received chemotherapy within 4 to 6 weeks after surgery in the same procedure as other patients. The remaining 34 patients initiated 8 cycles of chemotherapy after a 4-6-week rest while completing radiotherapy. The chemotherapy regimen consisted of 1.5 mg/m^2 vincristine a day given intravenously over 15 min on days 1 and 8, 750 mg/m^2 cyclophosphamide a day given intravenously over 3 h on days 1 and 2, and 75 mg/m^2 cisplatin a day given on day 1. A single dose of MTX at 12.5 mg (2.5mg per milliliter of 0.9% sodium chloride solution) was given on day 1 in MTX group, while control group received cerebrospinal fluid (CSF) cytology analysis alone. Brain magnetic resonance imaging (MRI) examination and spine MRT were performed routinely after two, four, six and eight cycles of chemotherapy for all patients.

Outcomes

The 5-year PFS was 70.99% (95% CI, 58.22%-90.42%) and the 5-year OS was 72.99% (95% CI, 60.41%-93.06%) for MTX group, while those for control group were 41.67% (95% CI, 17.93%-66.92%) and 50% (95% CI, 27.88%-77.14%), respectively. Upon Chi-square test, there was a significant difference in the excellent response rate between the two groups when comparing PFS and OS ($p < 0.05$).

OS was noted in children with R0 resection (HR: 0.48, 95% CI: 0.0053-33.29), M0 status (HR: 0.59, 95% CI: 0.00092-28.87), no diffuse anaplasia histology (HR: 0.14, 95% CI: 0.0058-1.53) and MTX intrathecal injection (HR: 0.49, 95% CI: 0.099-2.49).

In the meantime, PFS was noted among children with R0 resection (HR: 0.46, 95% CI: 0.0052-31.26), M0 status (HR: 0.44, 95% CI: 0.0069-21.49), no diffuse anaplasia histology (HR: 0.14, 95% CI: 0.0060-1.52) and MTX intrathecal injection (HR: 0.67, 95% CI: 0.141-3.39).

However, none of the above four factors was identified as the significant risk factors for OS or PFS ($p > 0.05$).

MTX-related acute leukoencephalopathy

Six (18.75%) of the 32 patients developed MTX-related acute leukoencephalopathy. The details of the six patients are presented in Table 1. The manifestation of acute leukoencephalopathy was so mild that only one patient (No. 1) suffered from alalia. Two patients (No.3, 4) were asymptomatic, and three (No.2, 5, 6) had fatigue that was not paid attention to until the diagnosis of leukoencephalopathy. Five patients (No.2, 3, 4, 5, 6) were diagnosed with leukoencephalopathy during routine MRI after 6, 4, 4, 4, 6 cycles of chemotherapy, respectively.

For patient No.1, tumor cells were present in the CSF after one cycle of chemotherapy. MTX (12.5 mg) was injected intravenously once a week for the antitumor purpose. Three single doses were administered to this patient totally during the interval between two cycles of chemotherapy. As the patient developed alalia soon, she could not continue her next cycle of chemotherapy. Brain MRI and brain vessel MRI were performed thereafter. Brain MRI revealed multiple lesions in the bilateral cerebellar hemispheres, thalamus, basal ganglia region, lateral ventricle, radial coronal, center semicovale, bilateral frontoparietal temporal lobe and right occipital lobe. T1 weighted imaging (T1W1) revealed slightly low signal (Figs. 1A), T2 weighted imaging (T2WI) showed high signal (Figs. 1B), while flair image presented slightly high signal with blurred boundary (Figs. 1B). Diffusion weighted imaging (DWI) suggested limited diffusion of some lesions (Figs. 1D and 1E), and enhanced MTI suggested mild enhancement of some white matter lesions (Figs. 1F). There was no obvious abnormality on brain vessel MRI (Figs. 1G and 1h). Oligoclonal band (OCB) analysis found the presence of immunoglobulin G (IgGs) in her CSF. Leukoencephalopathy was diagnosed, and she was

treated with intravenous methyl prednisolone at 2 mg/kg three times daily (which reduced over a 2-week period), oxygen support, and human blood albumin injection. Her condition was stable at the last follow-up.

In patient 2, screening MRI after the 6^{th} cycle of chemotherapy revealed several infiltrative lesions that involved the bilateral frontal, parietal, temporal lobes, right cerebellar hemisphere and left pontile. T1WI showed slightly low signal (Figs. 2A and 2D), T2WI displayed high signal (Figs. 2B and 2E), while flair image revealed slightly high signal (Figs. 2C and 2F). The largest size of the lesion was about 1.5 cm, which was located in the right cerebellar hemisphere. Magnetic resonance spectroscopy (MRS) revealed Cho/NAA=1.78 of the lesion in the right cerebellar hemisphere, while Cho/NAA=0.97 of the lesion around the left lateral ventricle. This finding led to the differential diagnosis of tumefactive demyelinating lesions and MB recurrence. Cerebral blood flow (CBF) was measured, but no abnormal signal was observed during CBF subsequently. Leukoencephalopathy was diagnosed thereafter. Therefore, dexamethasone at 10 mg/d and oxygen support were given at a local hospital. A month later, the abnormal signal in white matter area was slightly improved compared with before (Figs. 3A, 3B and 3C). But the lesions in the cerebellar hemisphere increased to 2.5 cm with contrast enhancement (Figs. 3D, 3E and 3F). MRS revealed Cho+Cr/NAA=5.3 of this lesion. Besides, CBF revealed multiple cerebral hyperperfusion lesions as well. Relapsed disease was considered. The patient died two weeks later.

For patients No.3, 4, 5, 6, the findings were similar to those of patient 1. All of these cases were alive with severe neurological symptoms.

None of the patients in control group developed acute leukoencephalopathy. With the exception of acute leukoencephalopathy, there was no difference in the high-grade toxicity rate (grade [?] 3) between the two groups.

Discussion

Although multiple drugs have been applied inanition to MTX, the acute neurotoxicity reported in cancer patients who are undergoing therapy is usually attributed to MTX. MTX is associated with clinical or neuroradiological evidence of leukoencephalopathy in survivors with childhood acute lymphoblastic leukemia (ALL) and CNS or head and neck tumors. It is reported that, the impaired low intelligence quotient (IQ) is strongly related to the reduced white matter volume in MB patients treated with chemotherapy and radiotherapy after surgery [7]. A study describes the long-term neurocognitive outcomes of young children with ALL receiving CNS-directed therapy consisting of chemoradiotherapy, high-dose intravenous MTX and very high-dose intravenous MTX in addition to intrathecal therapy. The results show that for young children with ALL, the avoidance of CRT is associated with good long-term neurocognitive outcomes, while the dose of intravenous MTX did not affect these outcomes[8]. As such, it has been recommended to reconsider the use of intrathecal MTX in the treatment of MB since then on.

However, dose these mean MTX intrathecal injection be totally avoided for the treatment of MB patients? Indeed, intrathecal MTX was an independent prognostic factor for good prognosis in our study, even though there was no statistical significance. R0 resection, none diffuse anaplasia histology and M0 status were all the independent predicting factors for good prognosis, as revealed by multivariate Cox proportional hazard analysis. But the p -values of all these three well-known factors showed no statistical significance, which might be correlated with the small sample size of the two groups.

Moreover, to our knowledge, till now, the best 5-year PFS of metastatic MB is 71%, with the addition of carboplatin at 35 mg/m^2 for 30 doses before daily radiotherapy[4]. For children with high-risk disease, the 5-year PFS of 62% to 70% has been reported after radiotherapy combined with a variety of chemotherapeutic agents used during and after radiotherapy[7, 9-11]. Typically, a 70% 5-year PFS was reported in the St. Jude prospective study that adopted post-radiotherapy high-dose chemotherapy and stem cell rescue[10]. In our study, the 5-year PFS was 70.99% and 5-year OS was 72.99% for MTX group. To be mentioned, there were 32 patients in MTX group, 28 of whom were included in molecular analyses. Except for the unknown molecular subtype of these 4 patients, none of the remaining cases belonged to WNT subtype, suggesting that about 10% of all MB patients had excellent prognosis[12]. The 5-year PFS for MTX group was 70.99%,

which improved upon the previously reported PFS, suggesting a benefit for patients who received intrathecal MTX combined with chemotherapy and radiotherapy. Moreover, our study also reported a good 5-year OS rate, and there were statistically significant differences in the 5-year PFS and 5-year OS between MTX and control groups.

Interestingly, all patients who developed acute leukoencephalopathy were uniformly group 4 MB females. Although the mechanism of MTX-related leukoencephalopathy remains unclear, several mechanisms have been proposed, for instance, certain gene polymorphisms such as single nucleotide polymorphisms in the methylenetetrahydrofolate reductase[13], glutathione S-transferase Pi 1genes[14] and ATP binding cassette subfamily B member 1[15]. Furthermore, a recent study implicates that adenosine receptors and high cumulative dose of systemic MTX administration are significantly associated with MTX-related leukoencephalopathy in patients with hematological malignancies[16]. However, no existing study has focused on the mechanisms of MTA in inducing leukoencephalopathy in MB patients. Leukoencephalopathy during active treatment was referred to as "acute leukoencephalopathy" in our study[17]. The biologic foundation of group 4 tumors is poorly understood, and the key alternation is KDM6A, a histone demethylase. In a study on triple negative breast cancer, recruitment of KDM6A leads to tumor recurrence. Inhibition of adenosine receptors A2BR delays tumor recurrence in vivo[18]. These results show that there may be some interaction between the two genes. It is necessary to delineate the molecular mechanism by which KDM6A is associated with adenosine receptors that leads to a susceptibility to acute leukoencephalopathy in group 4 MB. As such, taking into account the excellent 5-year PFS, it is recommended to add intrathecal MTX to high risk MB patients of both SHH and group 3 subgroups.

Nevertheless, several limitations should be noted in our study. This was a retrospective study, and the sample size (especially for control group) was quite small. Besides, compared with MTX group, patients in control group were diagnosed earlier when surgical techniques were worse in those days. R+ was quite common in control group, and it was impossible to make confident conclusions about the effect of incomplete resection on survival in this small cohort. Besides, long-term neurocognitive outcome data were limited to a small subset of patients.

Conflict of Interest statement: The authors indicated no potential conflicts of interest.

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Availability of data and materials: Patient's data were available in medical records room of the first hospital of Jilin university. The datasets generated and/or analysed during the current study are not publicly available due to they are files in medical records room in our hospital, but are available from the corresponding author on reasonable request.

Code availability : Not applicable

Ethics approval: Approved by the Ethical Institution of the first hospital of Jilin university.

Consent to participate: Because of its retrospective manner, informed consent was waived by the Ethical Institution of the first hospital of Jilin university

Consent for publication: Not applicable

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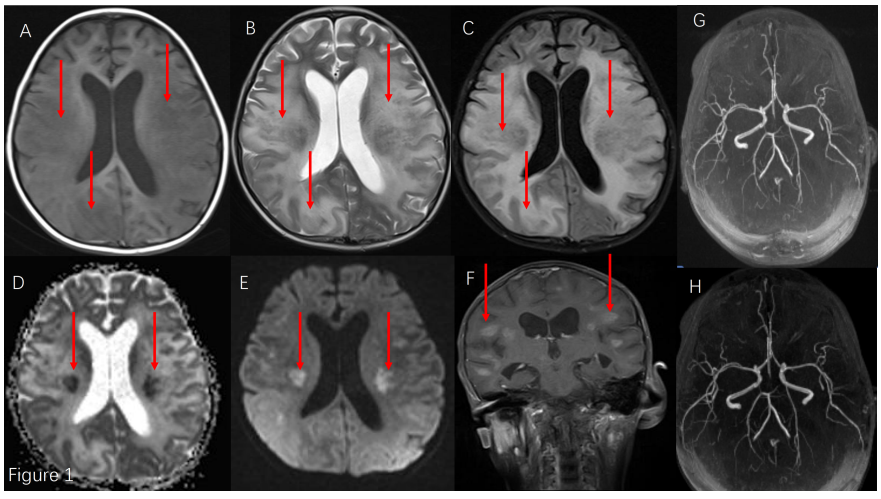
Figure legends:

Figure 1 : Brain MRI revealed multiple lesions in the bilateral cerebellar hemispheres, thalamus, basal ganglia region, lateral ventricle, radial coronal, center semicovale, bilateral frontoparietal temporal lobe and right occipital lobe. a: T1 weighted imaging (T1W1) revealed slightly low signal. b: T2 weighted imaging (T2WI) showed high signal. c: Flair image presented slightly high signal with blurred boundary. d and e:Diffusion weighted imaging (DWI) suggested limited diffusion of some lesions. f:Enhanced MTI suggested mild enhancement of some white matter lesions.g and h:There was no obvious abnormality on brain vessel MRI.

Figure 2 : Several infiltrative lesions involved the bilateral frontal, parietal, temporal lobes, right cerebellar hemisphere and left pontile of the patient 2. a and d: T1WI showed slightly low signal. b and e: T2WI displayed high signal. c and f: flair image revealed slightly high signal.

Figure 3 : Several infiltrative lesions involved the bilateral frontal, parietal, temporal lobes, right cerebellar hemisphere and left pontile of the patient 2 (1 month after treatment).a.b,c: the abnormal signal in white matter area was slightly improved compared with Figure 2. d,e,f: the cerebellar hemisphere showed a 2.5 cm with contrast enhancement.



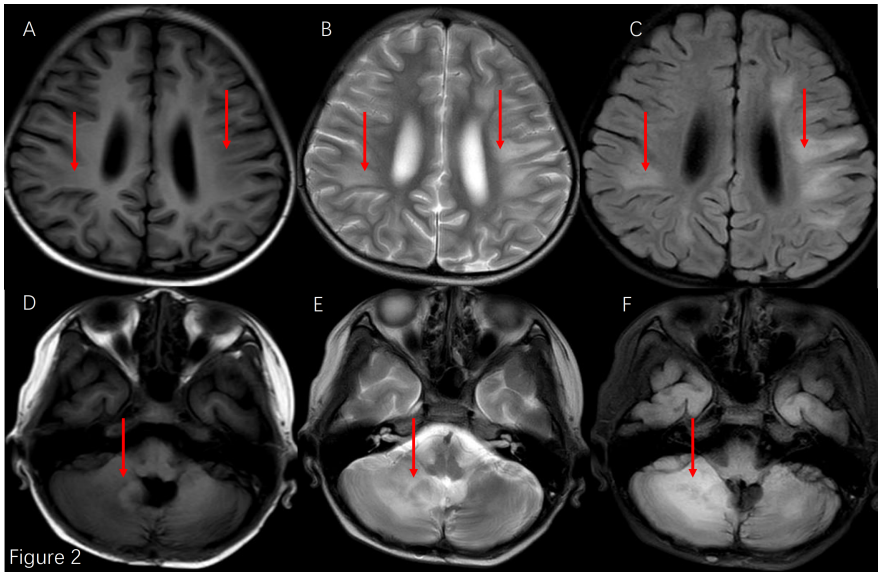


Figure 2

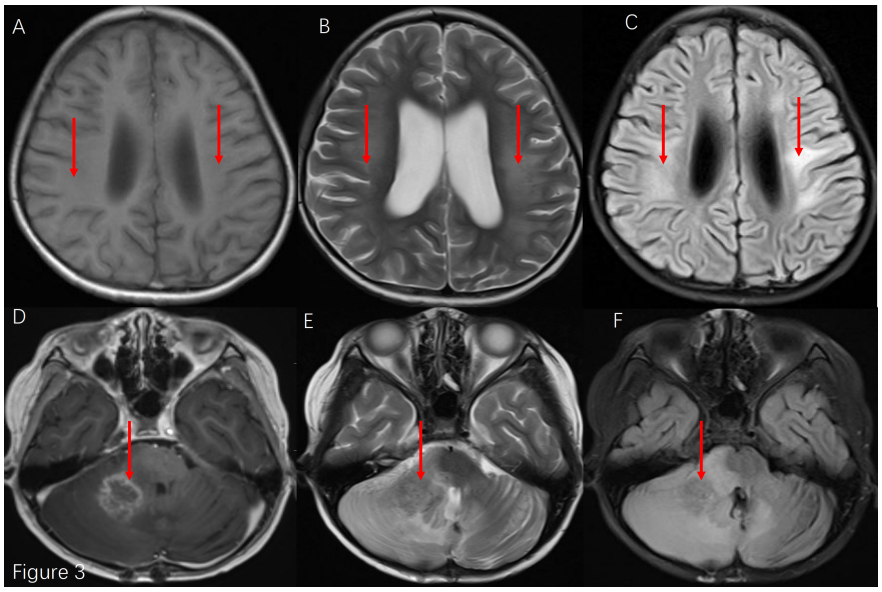


Figure 3

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