

Intrathecal chemotherapy for refractory disseminated medulloblastoma

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Abstract

Objective To analyze the effect of intrathecal (IT) chemotherapy for disseminated medulloblastoma.

Materials and methods Twenty-one patients received IT chemotherapy using the chemotherapeutic agents of methotrexate (MTX) and nitrosoureas (ACNU, MCNU) including nine patients for residual leptomeningeal lesions after initial surgery and radiation, and 12 for a recurrence with leptomeningeal dissemination. Of these 21 patients, 12 received a lumbar and/or ventricular bolus injection of the chemotherapeutic agents, one received the ventriculolumbar perfusion of the agents, and eight received both the perfusion and bolus injection. The doses ranged from 6–7 mg/m² of ACNU for perfusion and 3–3.5 mg/m² of ACNU, MCNU, or MTX for the bolus injection, and the cycles were administered from 3 to 12 times for perfusion and from 5 to 54 times for the bolus injection. The effects of chemotherapy were assessed by both radiological and cytological examinations, and the clinical symptoms were also assessed. Radiological and/or cytological responses were observed in 10 of 21 patients (47.6%), including seven cases demonstrating a complete remission. The 5-year overall survival rate and 5-year survival rate after dissemination were 61.5 and 46.4%, respectively. Five patients who received a lumbar bolus injection of nitro-

soureas experienced paraplegia and double incontinence. One patient who received a ventricular injection of nitrosoureas experienced truncal ataxia.

Conclusion IT chemotherapy was found to be effective in some cases with refractory disseminated medulloblastoma and it seems to be an appropriate treatment choice for leptomeningeal recurrence. However, the frequent bolus injections of nitrosoureas should be avoided to prevent the side effects.

Keywords Medulloblastoma · Dissemination · Intrathecal (IT) chemotherapy · Ventriculolumbar perfusion chemotherapy · Nitrosourea (ACNU · MCNU) · Methotrexate

Introduction

Treatment for recurrent medulloblastoma with leptomeningeal dissemination is very difficult and the prognosis of such refractory medulloblastoma patients tends to be extremely poor. No definitive treatment strategy has yet been established and we therefore usually choose high-dose chemotherapy, intrathecal (IT) chemotherapy [1–11], or additional radiotherapy depending on each individual case. As a standard procedure for medulloblastoma at our institute, craniospinal irradiation is performed as soon as possible after the maximum possible removal of the primary tumor. After these initial therapies, maintenance systemic chemotherapy using PE (CBDCA, VP-16) or ICE (IFOS, CDDP, VP-16) regimen is thereafter performed for about 2 years. During the course of these therapies, we have also performed IT chemotherapy aggressively for advanced stage disseminated medulloblastomas, such as leptomeningeal recurrences or residual leptomeningeal lesions since

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1979. In this study, we retrospectively analyzed the clinical data for patients with IT chemotherapy to evaluate the effectiveness of this unique adjuvant therapeutic option for disseminated medulloblastoma.

Materials and methods

Patients

From 1979 to 2005, 45 patients with medulloblastoma were treated with craniospinal irradiation and maintenance systemic chemotherapy after a surgical removal of the primary tumor. Of these 45 patients, 21 received IT chemotherapy including nine patients for residual leptomeningeal lesions after the initial surgery and radiation, and 12 patients for leptomeningeal recurrence after a complete remission. The patients included 14 males and 7 females. The patients ranged in age from 1 to 26 years (mean 10.9 years old). The interval between the diagnosis of the primary disease and the detection of the subarachnoid dissemination in cases of leptomeningeal recurrence ranged from 6 to 80 months (26 months of average). The primary tumors were confirmed to be medulloblastoma in all 21 patients based on a histopathological diagnosis. The diagnosis of subarachnoid dissemination was made based on cerebrospinal fluid (CSF) cytology, computed tomography and/or magnetic resonance imaging (MRI). The IT chemotherapeutic regimen was carefully explained to the patients and/or their family, and informed consent was obtained from all participating patients.

Of these 21 patients, 12 patients received a lumbar and ventricular bolus injection of the chemotherapeutic agents, one received ventriculolumbar perfusion of the agents, while eight received both the perfusion and the bolus injection. Systemic chemotherapy was combined in 17 cases while additional radiotherapy was combined in eight cases. The cycles ranged from 3 to 12 times for perfusion and from 5 to 54 times for the bolus injection (Table 1). All these data were obtained from the patients' records.

Table 1 Intrathecal (IT) chemotherapeutic regimens of the 21 patients with disseminated medulloblastoma

Number of patients (<i>n</i> =21)	IT Cx with systemic Cx (PE or ICE Cx)
12	Lumbar and/or ventricular bolus injection
1	Ventriculolumbar perfusion
8	Perfusion and bolus injection

Drug: ACNU/MCNU, MTX; dose: 6–7 mg/m² (perfusion), 3–3.5 mg/m² (bolus injection); cycle: 3–12 times (perfusion), 5–54 times (bolus injection)

Cx Chemotherapy, PE CBDCA + VP-16, ICE IFOS + CDDP + VP-16

Treatment

All patients had Ommaya's reservoirs established on one side of the lateral ventricle and the lumbar spinal canal beforehand. Before the start of the perfusion chemotherapy, the communication between the ventricular system and the subarachnoid space was anatomically confirmed by MRI and shunted cases did not receive this perfusion chemotherapy. On the other hand, in the previous shunted cases of the bolus injection, after drug administration, either the on-off valve was occluded or the adjustable valve was set to the highest pressure for several hours and then it was re-opened.

1. Perfusion chemotherapy

The patients lay in a lateral position and 6–7 mg/m² of ACNU(3-[(4-amino-2-methyl-5-pyrimidinyl)-methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride, nimustine) dissolved in 100 ml of lactated Ringer with 0.4 ml of 7.0% sodium bicarbonate and 10 mg of prednisolone (PSL) was drip infused into the ventricular reservoir and drained via the reservoir placed in the lumbar region at approximately the same rate as that of the infusion for about 60 min. Thereafter, the patients remained in a recumbent position for about 1 h before returning home. The perfusion was scheduled every 1 or 2 weeks on an outpatient basis.

2. Bolus injection

The patients were placed in a lateral position and after removing an equivalent volume of CSF (approximately 4 ml) from each ventricle and the lumbar reservoirs, 3–3.5 mg/m² of ACNU, MCNU (methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy- α -D-glucopyranoside, ranimustine) or MTX with 6–7 mg/m² of PSL dissolved in 2 ml of normal saline (NS) was bolus injected via Ommaya's reservoir of the lateral ventricle and the lumbar region and then it was flushed with 2 ml of NS. Next, the patients laid down flat in the supine position for about 1 h before returning home. The bolus injection was scheduled every 1 or 2 weeks on an outpatient basis.

Evaluation and response criteria

The effects of the chemotherapy were assessed by cranial and spinal MRI and CSF cytology, and also clinical symptoms were evaluated. A complete response (CR) was defined as the complete clearing of radiographic disease, and the malignant cells disappeared from the CSF. A partial response (PR) was defined as an improvement in the CSF findings and/or the neuroradiological findings. Where none of the parameters showed any change or showed changes for the worse, a classification of no change (NC) or progressive disease (PD) was assigned, respectively. The patients who showed CR or PR were considered to be responders when calculating the response rates. The

survival rates were estimated by the Kaplan–Meier method. In this study, 18 of those 21 patients underwent MRI before and after IT chemotherapy and 11 of those 21 underwent CSF cytology before and after IT chemotherapy.

Results

Response rate

The radiological and/or cytological responses were observed in 10 of the 21 patients (47.6%) including seven who demonstrated a complete remission. Seven of 18 patients who underwent MRI showed an improvement. They included four complete responses and three partial responses. Six of the 11 cases evaluated by CSF cytology achieved a clearance of malignant cells. The estimated 5-year overall survival rate after the diagnosis of primary tumor was 61.5% and 1-, 2-, and 5-year survival rates after the diagnosis of dissemination were 81.0, 61.9, and 46.4%, respectively (Fig. 1). The mean follow-up period of surviving patients was 11.4 years (range through 4.0 to 23.0 years).

Representative cases

The patient was a 12-year-old girl. The MRI of onset showed scattered spinal dissemination, whose initial Chang's stage was M3. After a surgical removal of the primary tumor and craniospinal irradiation, a complete remission was achieved. However, 2 years later, during the maintenance chemotherapy, spinal leptomeningeal dissemination recurred. Consequently, the patient received 10 courses of ACNU perfusion with systemic chemotherapy for about 5 months and a complete response was thus achieved according to both the MRI and cytological findings (Fig. 2, case 1:a–e).

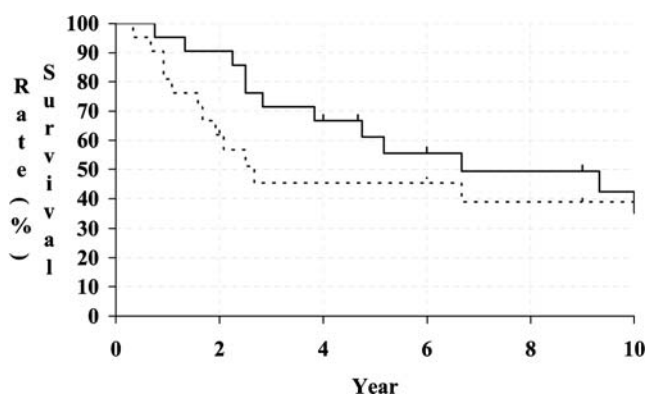


Fig. 1 Kaplan–Meier survival curves showing the overall survival (solid line) and survival after dissemination (dotted line)

Adverse events

Five patients who received a lumbar bolus injection of nitrosoureas more than seven times experienced paraplegia and double incontinence. One patient with 54 administrations of ventricular injection of nitrosoureas experienced truncal ataxia.

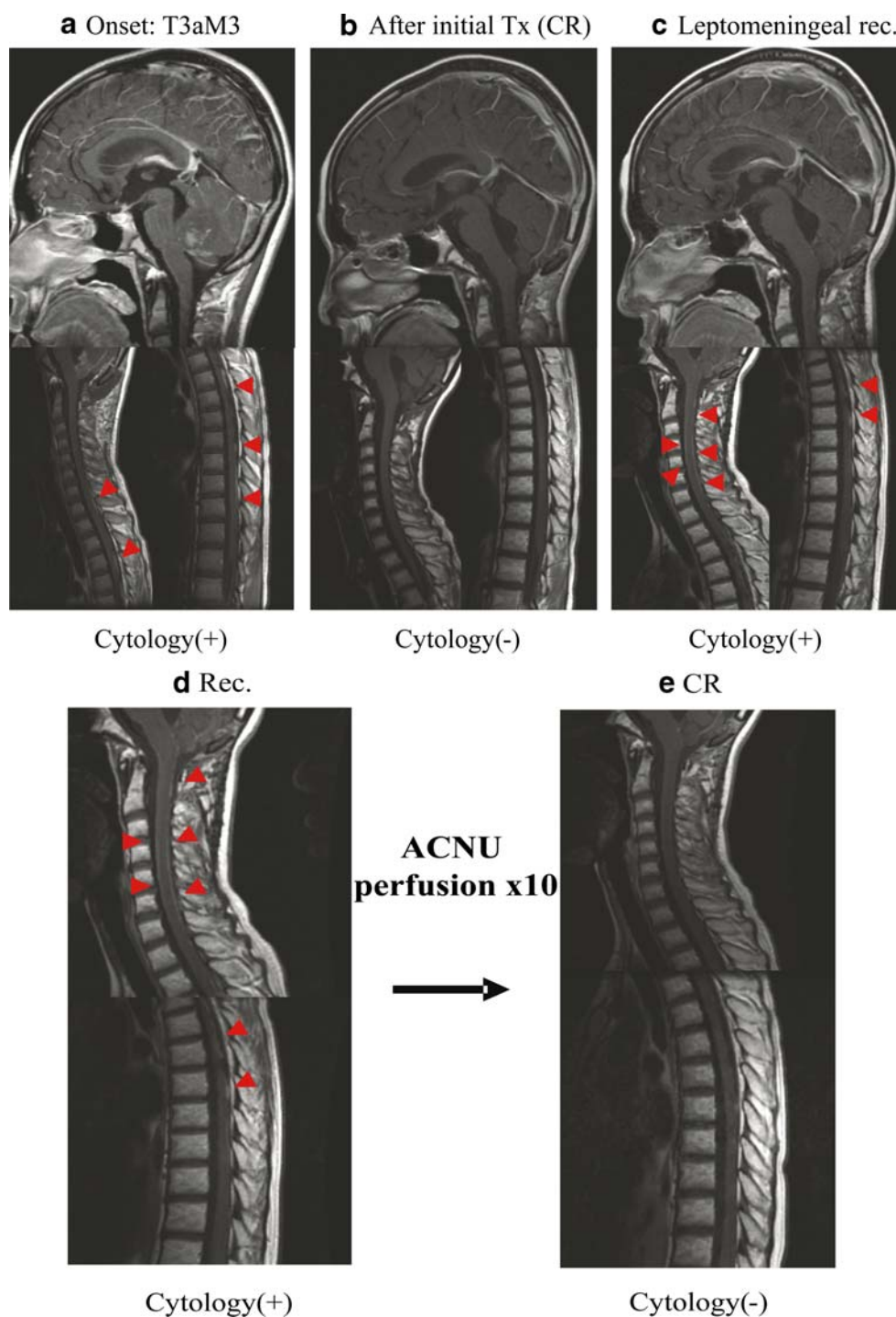
Discussion

Leptomeningeal dissemination is a serious and fatal state of malignant brain tumor and medulloblastoma frequently disseminates throughout the cerebrospinal fluid. The treatment of leptomeningeal dissemination of the medulloblastoma is very difficult and leptomeningeal recurrence is the most serious of all these conditions. Major treatments of leptomeningeal dissemination are craniospinal irradiation (CSI) including radiosurgery, systemic chemotherapy including high-dose chemotherapy with autologous bone marrow transplantation and intrathecal (IT) chemotherapy [1–11]. Medulloblastoma is a radiosensitive tumor, and irradiation is therefore considered to be an appropriate and effective treatment modality, but almost all patients had already undergone CSI as the initial therapy, as a result, the additional irradiated dose and fields are strictly limited because of the risk of radiation necrosis of the nervous tissue. Additional radiotherapy is usually limited to the palliative care of pain control or for temporary rescue in a case in which the long-term outcome is beyond consideration. On the other hand, we consider radiosurgery, such as the gamma knife, to be also useful for treating nodular intracranial disseminations, but it is an insufficient treatment for widespread CSF dissemination.

Systemic chemotherapy is necessary for the treatment of medulloblastoma and sometimes minute disseminations disappear as a result of conventional systemic chemotherapy, but sufficient drug delivery is not achieved across the blood-brain barrier. High-dose chemotherapy with bone marrow transplantation using peripheral blood stem cells is sometimes performed, but this method is usually performed one or two times because of limitations in collecting stem cells and after high-dose chemotherapy, maintenance systemic chemotherapy cannot be performed in most cases because of persistent myelosuppression. If high-dose chemotherapy does not eradicate the disseminated lesions, then a patient enters a lethal state due to a regrowth of the tumor; therefore, the indications for high-dose chemotherapy to treat leptomeningeal recurrence thus remain controversial.

IT chemotherapy is convenient, repeatable, and there are no systemic side effects such as myelosuppression. Theoretically, drug delivery is achieved for whole leptomeningeal lesions; therefore, IT chemotherapy appears to be the treatment of

Fig. 2 MRI scans showing the effects of IT chemotherapy. Case 1 **a** MRI of onset, **b** after the initial surgery and CSI, **c** leptomeningeal recurrence, **d** and **e** pre- and post-IT chemotherapy



choice for such patients. Unfortunately, the effect of conventional IT chemotherapy with MTX, cytosine arabinoside, and thio-TEPA is thought to only be temporary [2, 5, 6, 8, 9], and there has so far been no large clinical study, and thus the effect of IT chemotherapy has not been established. On the other hand, one clinical study produced an 88% response rate by ACNU perfusion for disseminated medulloblastoma and PNET [10]. Another study of IT chemotherapy of

Mafosfamide, a cyclophosphamide derivative, reported a 70% response rate [7]. In our study, about 50% of patients showed a clinical response. Seven patients achieved a complete remission and survived for a long time, and the 5-year survival rate after dissemination was 46.4%. The prognosis of the patients with disseminated medulloblastoma of noncomplete remission after initial treatment and leptomeningeal recurrence is thought to be extremely poor. IT

chemotherapy thus appears to be the treatment of choice for disseminated medulloblastoma. However, we have to pay attention to some difficult points when performing IT chemotherapy. At first, the combination of systemic chemotherapy is necessary because IT chemotherapy probably provides insufficient drug delivery into deep parenchymal invading lesions, and thus both the intrathecal-side and parenchymal-side drug delivery (like a sandwich) is needed for especially thick bulky disseminated lesions. Second, there is the problem of how to achieve a sufficient concentration of the drug in the subarachnoid space over the cerebral convexities. Because in the ventriculolumbar perfusion method, the drug is infused into the ventricle and it flows straight down the spinal subarachnoid space and then drains through the lumbar reservoir, and thus the drug concentration in the ventricle and spinal subarachnoid space is sufficient to achieve an appropriate therapeutic effect [3]. However, a sufficient retrograde drug flow from the cisterna magna to the cerebral convexity is difficult to obtain using this perfusion method. On the other hand, because of the short half-life of the nitrosoureas, a sufficient concentration of the drug in the whole meningeal field cannot be achieved by the bolus injection method. Therefore, another method is necessary to achieve a sufficient concentration of nitrosoureas in the subarachnoid space over the cerebral convexity. The other problem is myelotoxicity by a bolus injection of nitrosoureas into the lumbar spinal canal. In our study, a bolus injection of nitrosoureas (3–3.5 mg/m²) every 1 or 2 weeks and more than seven times bolus injection caused permanent myelotoxicity of paraplegia and double incontinence. Perfusion chemotherapy and up to 32 administrations of a ventricular bolus injection of nitrosoureas did not cause any permanent toxicity. In addition, a bolus injection of MTX into the ventricle and lumbar spinal canal did not cause any toxicity. Therefore, the high concentration of nitrosoureas in the lumbar spinal canal was thus considered to have caused myelotoxicity. The failure of sufficient diffusion of the drug is also related to the side effects because the myelotoxicity appeared in the lumbar or lower segment of the spinal cord and did not appear in either the thoracic or higher region. In addition, these patients received spinal irradiation of 24 to 36 Gy, so spinal radiation also can influence the susceptibility to such myelotoxicity. Based on these findings, to reduce myelotoxicity, a lower drug concentration can lessen the side effects because the concentration of perfusion (0.1 mg/ml) did not cause any toxicity. The Trendelenburg position after a bolus injection can improve the diffusion of the drug because the specific gravity of nitrosoureas (1.019; ACNU 5 mg in NS 2 ml) is heavier than that of CSF (1.005–1.009). Further studies on the administration methods, drug concentrations and drug

combinations are thus necessary to prevent side effects. Thus, from the view points of effectiveness and safety, ventriculolumbar perfusion, ventricular bolus injection, and several times of lumbar bolus injection of nitrosoureas are appropriate IT chemotherapy for refractory disseminated medulloblastoma at present.

Conclusion

IT chemotherapy is therefore considered to be effective in some cases with disseminated medulloblastoma and it thus seems to be an appropriate treatment choice for leptomeningeal recurrence. However, the frequent lumbar bolus injection of nitrosoureas should be avoided to prevent side effects. Further studies are therefore warranted to establish more effective treatment regimens.

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