



Octreotide in the therapy of recurrent medulloblastomas

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ABSTRACT

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BACKGROUND: *Recurrence of medulloblastoma appears after 30% to 40% of the surgeries. Different from primary medulloblastoma, in which five-year survival rate is 50%, the survival time of relapses much shorter and only 20% of the patients manage to survive a year. There is a logical need for additional methods of treatment of recurrent medulloblastomas. The aim of the study is to determine the effects of intracavitary and long-term subcutaneous application of Sandostatin (octreotide) on the recurrent medulloblastomas.*

METHODS: *Fourteen children aged 4 to 9 years, in which, despite of craniospinal irradiation and chemotherapy came to a recurrence of medulloblastoma during the first 6 months after the surgery, were treated subcutaneously with Sandostatin (octreotide) in a longer period of time. Cerebellar medulloblastomas with a diameter bigger than 20 mm and spinal over 10 mm were removed operatively and octreotide with Beriplast was applied intracavitary.*

RESULTS: *Magnetic resonance of craniocaxis shows that the application of octreotide has caused the disappearance of spinal drop metastases in all 7 patients and the cerebellar metastases smaller than 5 mm in all 4 patients. Subcutaneous application of octreotide combined with intracavitary expresses an antitumoral effect in 2/3 of the relapses. The application of octreotide results with a transformation of Chang's stage M0 into M1 in 71.43% of the patients.*

CONCLUSION: *In the case of in loco or metastatic recurrence of medulloblastomas, intracavitary and subcutaneously applied octreotide results with a regression of the tumor in a 3 year time within 2/3 of the treated patients.*

KEY WORDS: *Medulloblastoma; Neoplasm Recurrence, Local; Octreotide; Treatment Outcome; Neoplasm Metastasis; Injections, Intraventricular; Administration, Cutaneous*

INTRODUCTION

Medulloblastoma is the most frequent embryonic tumor of the central nervous system (CNS), which appears before the 10th year of life in 75% of the cases, and twice more often in boys (1). Recurrence of medulloblastoma appears in 30%-40% of the operated patients, most frequently on the position of the previous surgery. A medulloblastoma can reach the spinal cord or other parts of the CNS by the dissemination of the cerebrospinal liquid, while the disseminations out of CNS are very rare. Medical response to a recurrence is a new surgery and an aggressive irradiation and cytostatic therapy on the complete craniocaxis. Certain number of children does not manage to stand the complete therapy, and those who do stand it, have severe problems, especially in neurocognitive functions, concentration, and intelligence (2-5). Different from primary medulloblastoma, in which five-year survival rate is 50%, the survival time of recurrence is much shorter, and only 20% of the patients manage to survive a year. There is a logical need for additional methods of treatment of recurrent medulloblastomas. Certain peptidomimetics such as synthetic somatostatin (octreotide) can reduce the level of intracellular cAMP for more than 70% by

direct activation of specific receptors on the tumor cells. They can also increase the activity of potassium (K) pump through triggering hyperpolarization of the cell membrane, disabling the potassium to enter the cytosol, what blocks numerous enzymatic systems and lead the cell into apoptosis (6). Adding the already known indirect antitumor mechanism of octreotide based on the suppression of neovascularisation and lower secreting of growth factors (growth factor, secretin, gastrin...) which are used by the tumor for its growth, initiates the idea of testing octreotide in the therapy of incompletely resected medulloblastomas or their metastases.

The aim of the study was to determine the effects of intracavitary and long-term subcutaneous application of Sandostatin on medulloblastoma recurrences and metastases, from the aspect of influence on tumor growth or involution. The task was also to evident eventual difference in effects, depending on the method of octreotide application.

PATIENTS AND METHODS

The study observes 14 patients (9 boys and 5 girls), aged 4 to 9 years (average 6), who developed a recurrence of medulloblastoma during the first 6 months after a surgery of a

primary medulloblastoma on the position treated in the previous surgery or elsewhere in the CNS. According to the SIOF criteria, all of the patients belonged to the group of high-risk medulloblastomas, and after the primary surgery had a full BCNU protocol and irradiation of craniaxis of 35Gy. Recurrences of the fossa posterior with a diameter bigger than 20 mm and spinal medulloblastomas with a diameter bigger than 10 mm were operatively removed and at the same time, octreotide mixed with Beriplast (1:2) was applied. The total volume of the depot medicament was determined according to the following original formula:

$$V_{(ml)} = 0.4185 \times a \times b \times c / a + b + c$$

where a, b, and c are the preoperative measures of each tumor in the 3 planes seen in a post contrast computer tomography (CT) scan or magnetic resonance (MR). The surgeries of recurrences were conducted only in prone position, in order to minimize the risk of descendent tumor dissemination by the cerebrospinal fluid (CSF).

Starting from the postoperative day one, patients received a subcutaneous application of Sandostatin in separate doses of 200 micrograms, 3 times a day, during the following 3 weeks. From the 2nd month on, every 15th day they received 30 mg of Sandostatin LAR - into the inguinal region.

Metastases smaller than 5 mm and drop metastases were treated only by subcutaneous application of octreotide. Oncological treatment was not repeated because of the short interval since its end. The following up term lasted 2-4 (average 3) years. The effects of the therapy were monitored by:

1) MR or CT (complete effect (CE)= removal of the tumor, partial effect (PE)=reduction of tumor's volume for more than 25%, stabilization effect (SE)= reduction of growth of tumor's volume for less than 25% and no effect (NE)= growth of tumor's volume for more than 25% or emerging of new metastases). During the first year since the evidencing of recurrence, a control MR of craniaxis was done every 3 months and later every six months. During the third year of the monitoring of the patients with an isolated recurrence of cerebellar medulloblastoma, one control was done with a contrast CT of brain.

2) Analysis of cerebrospinal fluid on the presence of the tumor cells on the surgery day and once in 3 months by lumbar puncture in the first year since the beginning of the therapy by octreotide, and later once in 6 months (M0 - without tumor cells, M1 - with tumor cells).

RESULTS

Chang's "M stage" has shown in 14 recurrences of medulloblastoma: M4 in 7 (50%), M3 in 4 (28.60%) and M2 in 3 (21.40%) patients (Table 1). Out of 8 patients with cerebellar medulloblastoma recurrences, isolated existence of recurrence on the place of previous medulloblastoma was recorded in only one patient. The existence of cerebellar medulloblastoma recurrence in the remaining 7 patients was followed by additional localizations of medulloblastoma. Out of 14 patients with medulloblastoma recurrence, spinal drop metastases were recorded in 8 patients and spinal metastases bigger than 5 mm in cervical or thoracic region were found in 6 patients. Medulloblastoma metastases of fossa cranii posterior (FCP) were recorded in 4 patients, in 2 of which, they were the only signs of the recurrence. One patient had a relapse in the position which was previously operated, an intramedullar metastasis in the cervical (C4-C7) and thoracolumbar region (Th3-4) region, and numerous drop metastases inside of the thoracolumbar region of the spinal cord at the same time.

Table 1. Effects of the treatment of recurrent medulloblastomas with intracavitary and subcutaneous application of octreotide

Patient	Gender	Effects of the treatment with Octreotide				CSFTC (M0, M1)
		FPR	FPM	SM DropM	SM ≥5mm	
1	f	CE*		CE		M1/M0
2	m		CE			M1/M0
3	f			CE		M1/M0
4	m		CE		NE	M1/M1
5	m	CE*	CE	CE	SE	M1/M0
6	f	SE*				M0/M0
7	m	NE			PE	M0/M1
8	m			CE		M1/M0
9	f	CE*		CE		M1/M0
10	m	NE		CE	NE	M1/M1
11	m	CE*		CE		M1/M0
12	f	PE*	CE			M1/M1
13	m				CE*	M1/M0
14	m				CE*	M1/M0

FPR (fossa posterior recidive); FPM (fossa posterior metastasis); SM (spinal metastasis); DropM (drop metastasis); CSFTC (cerebrospinal fluid tumor cells- (M1) exist or do not exist (M0)), CE (complete effect); PE (partial effect); SE (stabilizing effect); NE (no effect); * (intracavitary application of Octreotide)

The application of octreotide resulted with a total disappearance of spinal drop metastases in all 7 patients after six months (Table 1, Figure 1). Drop metastases and metastases with a diameter ≤5 mm in FCP completely involuted in all 4 patients (Figure 2, p<0.001). Spinal metastases bigger than 5 mm did not give any significant therapy response to the long-term subcutaneous application of octreotide, except of the cases of microsurgical removal of medulloblastoma recurrence and intracavitary application of octreotide (Table 1, Figure 3). Intracavitary application of octreotide resulted in 2/3 of the patients with a microsurgical resection of the cerebellar recurrence of the medulloblastoma - an absolute disappearance of tumors on the control scan, which were made in the 6th and the following months, while the remaining 1/3 expressed of partial reduction of the size or its stabilization (Table 1, Figure 4). Long-term subcutaneous application of octreotide without the intracavitary application of the same medicament did not prevent the progression of cerebellar rest-recurrence.

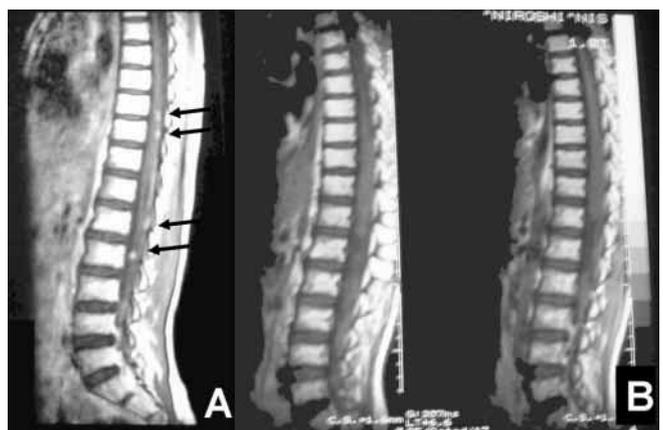


Figure 1. MR of thoracolumbar spine in a patient with medulloblastoma drop metastases: A) Numerous drop metastases in the spinal cord; B) Absence of visible drop metastases 6 months after a six-month octreotide therapy

During the analysis of CSF in purpose of Chang's M staging, a transformation of M1 into M0 in the 6th month was recorded, and showed a trend of persistence in 10 (71.43%) of 14 patients, and the same transformation was totally missing in all patients with a recurrence or a metastasis larger than 5 mm, unless they were treated by intracavitary application of Beriplast and octreotide (Table 1, p<0.001).

During a 3-year monitoring period there was only one death, and it was recorded in the 27th month since the recurrence was evidenced, in a nine-year old boy with a cerebellar recurrence and a thoracic metastasis larger than 5 mm, which did not fulfill the conditions for intracavitary application of octreotide.

Intracavitary application of octreotide in one patient was followed by signs of local obstruction of the circulation of cerebrospinal fluid, for that reason a ventriculoperitoneal shunt was installed. No local intolerant reactions or significant gastrointestinal problems were recorded during the subcutaneous application of octreotide.

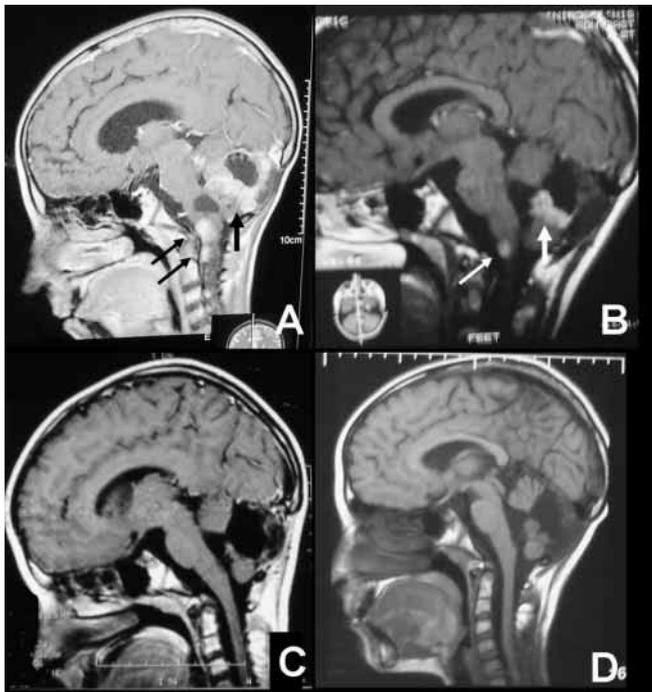


Figure 2. MR of brain in a patient with a cerebellar medulloblastoma recurrence WHO gr. IV and medulloblastoma metastases in the brain stem: A) Before the surgery, a big cerebellar medulloblastoma with a necrotic zone (thick arrow) and two smaller metastases (narrow arrows) are visible. B) Three months after removing the recurrence and an intracavitary application of octreotide, the mass of the medulloblastoma in the tumor cavity (thick arrow) is smaller, there is one metastasis less in the brain stem, and another one is reduced. C) 6 months after the surgery and the octreotide treatment, there are no remaining of medulloblastoma. D) 2 years after the surgery and the octreotide treatment, there are still no signs of relapse

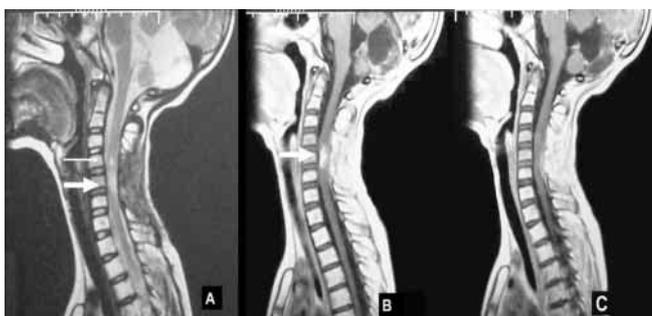


Figure 3. MR of the craniaxis 16 months after the cerebellar medulloblastoma surgery, and 6 months after a cervical metastasis surgery: A) cervical recurrence over 5 mm (thick arrow) and a satellite drop metastasis (narrow arrow) before intracavitary application of octreotide; B) 3 months since the beginning of the octreotide treatment, there is no longer a cervical drop metastasis, and the cervical recurrence is smaller; C) 6 months since the beginning of the octreotide application the cervical recurrence has totally involuted

DISCUSSION

It is an up-to-date doctrine to treat recurrent medulloblastomas with an aggressive oncological therapy. High-dose chemotherapy with the accompanied autologous transplantation

of stem cells offers encouraging results in the treatment of recurrent medulloblastomas (7,8).

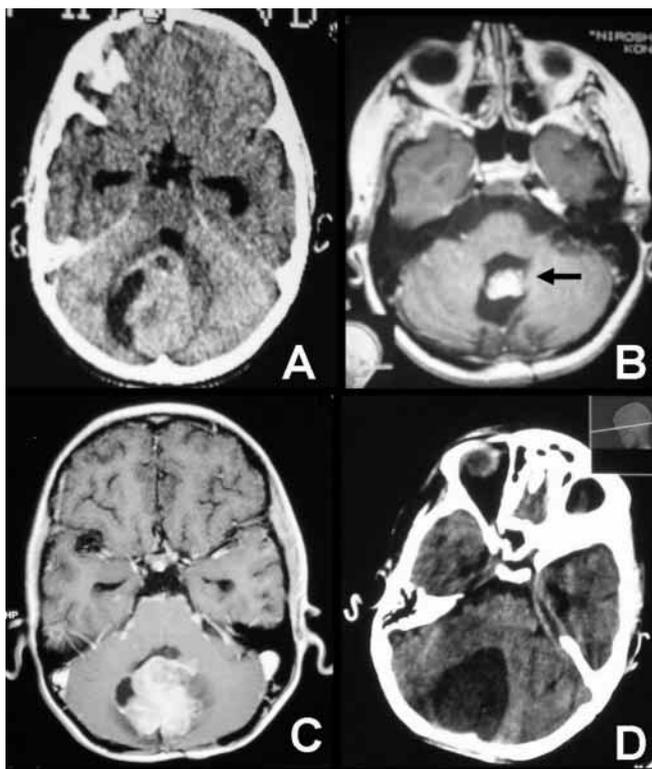


Figure 4. Cerebellar medulloblastoma before and after the relapse: A) CT of brain in a four-year old-boy with a primary medulloblastoma WHO grade IV; B) MR of brain 3 months after a primary medulloblastoma surgery (the arrow marks the signs of an initial recurrence); C) MR of brain 6 months after a primary cerebellar medulloblastoma surgery (the recurrence has the size of the primary tumor); D) CT of brain 2 years after the medulloblastoma recurrence surgery an intracavitary and subcutaneous application of octreotide (there are still no signs of a new relapse)

Intraoperative application of MR can contribute to a more complete resection of the tumor. Unfortunately, a medulloblastoma often approaches the bottom of the fourth ventricle and a part of brain stem. The border between the medulloblastoma and the neighboring tissues is an additional risk for the recurrence of the tumor and its dissemination. Therefore, finding of new therapy possibilities which do not have significant side effects is very important in prolonging of the period before the recurrence.

A characteristic of medulloblastoma cells is high presence of somatostatin receptors type 2 (SSR2). Through their activation, the level of cell ATP, synthesis of nucleic acids and complete metabolic activity of the cell are reduced, and the final outcome of those processes is the apoptosis of the tumor cell (9).

The disappearance of spinal drop and cerebellar metastases smaller than 5 mm fully suits the described antitumor effect of octreotide (a synthetic analog of somatostatin). The combined application of octreotide with long-term subcutaneous application and intracavitary depot application accomplishes a powerful apoptotic effect on the cells of the medulloblastoma, even in the cerebrospinal fluid. A scarce vascularization of medulloblastoma in comparison with malignant gliomas reduces the level of its penetration in deeper parts of the tumor. Therefore the medulloblastomas with a diameter bigger than 5 mm do not give an adequate therapy response to the subcutaneous application of depot octreotide.

Intracavitary application of fibrin glue Beriplast with successive degradation does not only enable a several week local presence of octreotide, but also reduces the dissemination of the cells of the medulloblastoma into the cerebrospinal fluid by the adhesive mechanism.

Prone position during the surgery, combined with intracavitary application of depot octreotide, can significantly prevent emerging of spinal metastases.

The absence of complications in prolonged subcutaneous application of octreotide with an evident positive effect in suppression of recurrent medulloblastomas is the best recommendation for its implementation.

CONCLUSION

Prolonged subcutaneous application of octreotide results with a disappearance of all smaller metastases of medulloblastomas. Subcutaneous application of octreotide in the therapy for medulloblastoma recurrences or metastases bigger than 5 mm causes no significant antitumor effects. Intracavitary application of depot octreotide is an appropriate way of long-term increasing penetration of octreotide into deeper parts of medulloblastoma rests and increases octreotide's antitumor effect. Medulloblastoma recurrences and metastases with a diameter bigger than 5 mm, apart from prolonged subcutaneous application of octreotide demand a surgical resection of recurrence and an intracavitary application of depot octreotide. The size of the sample of this study is limited by medulloblastoma's small participation in the number of all CNS tumors, as well as by the small number of primary verified metastases. The initial results in the prolonged intracavitary application combined with intracavitary application show that octreotide could be a useful adding to the existing surgical and oncological therapy of highly malignant medulloblastomas and their metastases. Further studies involving a bigger number of medulloblastomas in which the results of octreotide application could be correlated with the density of somatostatin-specific receptors, especially SSR type 2, could in a more exact way approve or deny the antitumor effect of octreotide notified in this study.

Octreotide is recommended as a powerful additional therapy, together with surgical, irradiation and high-dose chemotherapy, at the moment of the diagnosis of a primary high-risk medulloblastoma, and especially in case of its recurrence or a metastasis.

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