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THE APPLICATION OF SANDOSTATIN IN THERAPY OF HIGH-RISK MEDULLOBLASTOMAS

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Summary. *The praxis of early irradiation therapy and multimodal pre- and post-irradiation chemotherapy does not significantly prolong the five-year survival time in high-risk medulloblastomas. Aim – determination of the effects of intracavitary and subcutaneous application of the long active form of Sandostatin-Octreotide in treatment of high-risk medulloblastomas of fossa cranii posterior and its metastases. Patients and methods – 11 children (7 boys and 4 girls), average age 6.7 (4-11) years, who belonged to the group of high-risk medulloblastomas according to the SIOP criteria, were operated on and Octreotide was applied intracavitarily. All were additionally treated by subcutaneous application of Sandostatin. Effects of Octreotide on the rest of the tumor and the drop metastases were determined during the following 4-7 years (average 5), by NMR, cytologic examination of cerebrospinal fluid for the presence of tumor cells and survival time.*
Subcutaneous six-month application of Octreotide resulted in involution of cerebellar and all spinal drop metastases, while metastases bigger than 5mm were not significantly affected. Subcutaneous together with intracavitary application of Sandostatin inhibits the growth of medulloblastomas and leads to their involution in 2/3 of the patients with rest medulloblastoma of the cerebellum and medulla spinalis. Conversion of M1 into M0 was recorded in 8 (72.7%) cases, and a five-year survival time in 9 (81.8%) cases.
Subcutaneous application of Sandostatin for several weeks results in the apoptosis of malignant cells of medulloblastoma in a majority of patients. In loco application of Sandostatin combined with long term subcutaneous depot application can significantly inhibit the growth of medulloblastoma.

Key words: *High-risk medulloblastoma, sandostatin, intracavitary and subcutaneous therapy, drop metastases*

Introduction

Medulloblastoma is a malignant invasive embryonic tumor of the cerebellum with the possibility of dissemination within the CNS. It is the most frequent tumor in children, with the peak of incidence in the seventh year of life. According to the SIOP criteria (International Society of Pediatric Oncology), the existence of medulloblastoma in children younger than 4 years, subtotal resection, invasion of the brain stem (T3b and T4 according to Chang), presence of tumor cells in the cerebrospinal fluid (CSF) puts them into the group of high-risk medulloblastomas (1-3). Unlike low-risk medulloblastomas the five-year survival time of which is 70%, the survival time in high-risk medulloblastomas does not exceed 40%, irrespective of the application of the technique of prolonged mielosuppression by early irradiation and pre- and post-irradiation chemotherapy. Progression of the disease after a full oncology treatment opens the question of the adjuvant therapy (4).

Aim

The aim of the study is to examine the effects of Sandostatin (Octreotide) applied *in loco* and/or subcutaneously in patients classified as a group of high-risk medulloblastomas.

Material and Methods

Eleven patients (7 boys and 4 girls), aged 4-11 (average 6.7), who were classified into the group of high-risk medulloblastomas according to the SIOP criteria, received craniospinal irradiation and chemotherapy according to the standard oncology protocol, one month after the operation of the fossa cranii posterior (FCP). The tumor cavity of the medulloblastoma was wrapped intra-operatively using in a special method. The thickness of the depot suspension was calculated at 1 mm. The total volume of the depot suspension was 1.5-3.5 ml and calculated in accordance with the original formula given in (1):

$$V_{(ml)} = 0.4185 \times a \times b \times c \,/\, a + b + c \qquad (1)$$

where *a*, *b* and *c* are the preoperative measures of each tumor in three planes seen in a post-contrast CT scan or NMR.

Starting from postoperative day one, the patients were given Sandostatin subcutaneously in separate doses of 200 micrograms, three times daily, over the next three weeks. From the second month on, every 15 days, they received 30mg of Sandostatin LAR subcutaneously. The follow-up period lasted for 4-7 years (average 5).

The effects of the therapy were monitored by:

1) NMR (complete effect (CE) = removal of the tumor; partial effect (PE) = reduction of the tumor's volume by more than 25%; stabilization effect (SE) = reduction or growth of the tumor's volume by less than 25%; and, no effect (NE) = growth of the tumor's volume by more than 25% or emerging of new metastases;
2) Analysis of the cerebrospinal fluid for the presence of tumor cells once in 3 months by lumbar puncture.

Results

Out of 6 patients with subtotal resection of medulloblastoma of fossa cranii posterior, regression and total involution of medulloblastoma (CE) was recorded in 4 patients (Fig. 1), while SE was recorded in one patient and BE in one patient (Table 1).

Table 1. Effects of the treatment of high-risk medulloblastomas intracavitary and subcutaneously by Sandostatin

Patient	Gender	Effects of treatment with Sandostatin				
		FPT-rest	FPM	SM		CSFTC
				drop	≥5mm	(M_0, M_1)
1.	F	CE		CE		M_1/M_0
2.	M		CE			M_1/M_0
3.	F			CE		M_1/M_0
4.	M				NE	M_1/M_1
5.	M	CE			CE	M_1/M_0
6.	F	SE				M_0/M_0
7.	M	NE			PE	M_0/M_1
8.	M			CE		M_1/M_0
9.	f	CE		CE		M_1/M_0
10.	m			CE		M_1/M_1
11.	m	CE		CE		M_1/M_0

FPT rest = fossa posterior tumor rest;
FPM = fossa posterior metastasis;
SM = spinal metastasis; drop = drop metastasis;
CSFTC = cerebrospinal fluid tumor cells-exist (M_1) or do not exist (M_0);0
CE = complete effect; PE = partial effect; SE = stabilizing effect;
NE = no effect.

Out of 11 patients with drop metastases with high-risk medulloblastomas, spinal metastases were found in 9 cases, 6 of which with drop metastases, and 3 with spinal metastases ≥ 5mm. In all patients with drop metastases in the medulla spinalis, a total removal (CE) was recorded in the monitoring period (Fig. 2), while in patients with spinal metastases ≥ 5mm, CE (total involution of rest cervical metastasis) was recorded in one case after surgery and intracavitary application of Sandostatin (Fig.3). SE was also recorded in one case. No effect (NE) was recorded in one patient with thoracally located metastasis of an approximately 11mm diameter. Fossa posterior drop metastasis recorded in one patient disappeared after the six-month treatment with Sandostatin (CE) (Fig. 1).

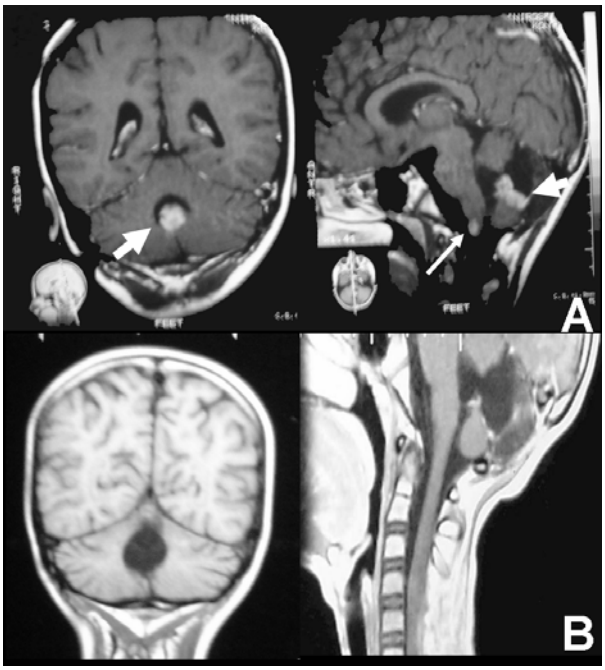

Fig. 1. Post-contrast coronal and sagittal NMR T1-weighted image shows:
A) Rest cerebellar medulloblastoma (thick arrow) and a drop metastasis in the brain stem (thin arrow).
B) Complete disappearance of rest cerebellar medulloblastoma and metastasis of the brain stem after cerebellar intracavitary and six-month subcutaneous application of Sandostatin.

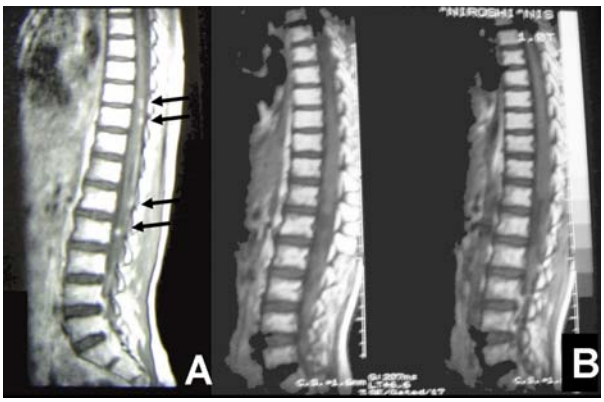

Fig. 2. Sagittal NMR imaging in a patient with multiple drop metastases in the spinal cord:
A) Multiple intra- and extra-medullar drop metastases of the thoracolumbar region (arrows)
B) Complete disappearance of spinal drop metastases after a six-month subcutaneous application of Sandostatin.

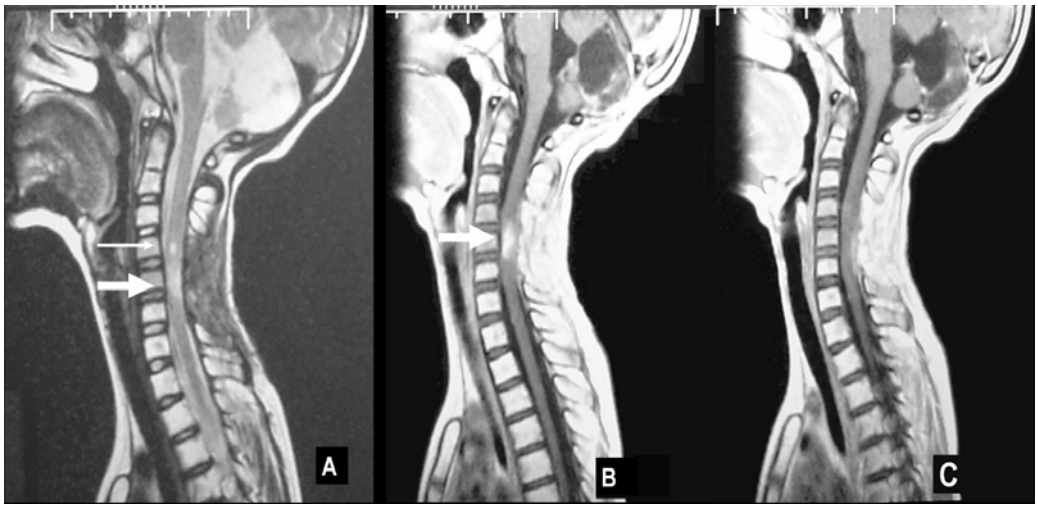

Fig. 3. Sagittal NMR imaging in a patient two years after a cerebellar medulloblastoma surgery, after a recent spinal macrometastasis surgery and *in loco* application of Sandostatin shows the following effects:
A) Presence of intra-medullar drop metastasis in C4 level and a significant intra-medullar rest medulloblastoma in C5 level.
B) After an intracavitary and 3-month subcutaneous application of Sandostatin, the cervical drop metastasis disappears and the C5 macrometastasis has a smaller diameter
C) After a 6-month Sandostatin treatment in the cervical part of the spinal cord and medulla, there are no signs of the presence of medulloblastoma.
Posterior fossa does not show signs of a cerebellar medulloblastoma residue.

The cytological examination of CSF in the patients treated by Somatostatin showed a total conversion into CSF without tumor cells (M_0), which is time-correlated with the moment of disappearance of the tumor on the NMR. Despite Sandostatin treatment, the presence of tumor cells was recorded in CSF (M_1) in 3 patients (27.27%). Two of these also had M_1 before Sandostatin treatment. A *de novo* appearance of tumor cells in CSF was recorded in only one patient, who, besides the post-operative rest tumor of the fossa cranii posterior, also had a metastasis, diameter 14mm, in the cervical part of the medulla spinalis. This patient died in the 47th month following the operation. The second death was recorded in a patient who showed a characteristic appearance of new spinal drop metastases and growth of the existing ones from 2-5mm (NE). Therefore, the five-year survival time in high-risk medulloblastoma patients who received Sandostatin *in loco* and subcutaneously was estimated at 81.81%. No surgically significant complications such as hydrocephalus, cerebellar abscess, retention cysts, or local allergic reaction were recorded. There was no evidence, either, of mielosuppression and severe hormonal disturbance. One patient suffered from diarrhea, which was eliminated by a two-day medical treatment.

Discussion

It is well-known that 50% of patients with medulloblastomas have chromosomal aberrations such as chromosome deletion 6q, 9q, 10q, 11q, 11q and 16q, as well as the existence of isochromosome 17q [i(17q)] (5). Unfortunately, there are still no practical results on gene therapy of this disease. Although early craniospinal irradiation with a total dose of 60Gy, combined with pre- and post-irradiation therapy has raised the level of the five-year survival to 65%, there is evidence of the third grade mielosuppression in 60% of these patients, which limits the duration of this therapy (6,7).

Other studies are also employing chemotherapy applied directly into the cerebrospinal fluid. An autologous bone marrow transplant or a peripheral stem cell rescue, with the growth factors that stimulate white blood cell production, are being utilized now and must be closely evaluated for overall safety (8).

Subcutaneous application of Sandostatin has shown a high level of efficacy in the involution of smaller (drop) metastases, while it partially reduces or influences the stagnation of the growth of metastases larger than 5mm.

A combined application of Sandostatin (subcutaneous and *in loco*) exerts a strong anti-tumor effect and results in a postoperative involution of bigger rest tumors. The apoptotic effect of Sandostatin on the cells of medulloblastoma is particularly obvious in cases of M_1 to M_0 conversion of CSF. This effect is obvious after six months of Sandostatin therapy. The absence of complications during Sandostatin therapy makes it most appropriate for adjuvant treatments of high-risk medulloblastoma.

The strong anti-tumor effect of Sandostatin is explained by the activation of SSR type 2 on the surface of tumor cells. Therefore, adding Sandostatin to the present surgical and oncology therapy would enable the immuno-suppression of the growth of medulloblastomas and the involution of drop metastases. The fact that Sandostatin does not trigger mielosuppression opens the possibility of preoperative prevention of the spinal dissemination of medulloblastomas.

Conclusion

1. A several-week subcutaneous application of Sandostatin results in the apoptosis of malignant cells of medulloblastoma and complete regression of drop metastases in a majority of patients

2. Intracavitary application of Sandostatin combined with subcutaneous depot Sandostatin (LAR) application can significantly inhibit the growth of medulloblastoma.

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PRIMENA SANDOSTATINA U TERAPIJI VISOKORIZIČNIH MEDULOBLASTOMA

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Kratak sadržaj: *Rana iradijaciona terapija i multimodalitetna pre i post iradijaciona hemoterapija do sada nisu značajnije produžili petogodišnje preživljavanje u visokorizičnih meduloblastoma.*
Cilj rada – procena efekta intrakavitarne i subkutane primene dugoaktivne forme Sandostatina-Octreotida u lečenju visokorizičnih meduloblastoma fose cranii posterior i njegovih metastaza.
Material i metode – jedanaestoro dece (7 dečaka, 4 devojčice), srednje starosti 6,7 godina (4-11), koji su prema SIOP kriterijumima pripadali grupi visokorizičnih meduloblastoma, operativno je lečeno, a intrakavitarno aplikovan Octreotid. Svi su dodatno tretirani subkutanom aplikacijom Sandostatina. Efekti Octreotida na rest tumora i drop metastaze određivani su narednih 4-7 godina (prosečno 5) putem NMR, citološkog pregleda likvora na prisustvo tumorskih ćelija i dužine preživljavanja.
Subkutana šestomesečna aplikacija Octreotida rezultovala je involucijom cerebelarne i svih spinalnih drop metastaza, dok na metastaze veće od 5 mm nije bitnije uticala. Subkutana aplikacija Octreotida udružena sa intrakavitarnom, suprimira rast meduloblastoma i dovodi do njegove involucije u 2/3 pacijenata sa restom meduloblastoma cerebeluma i kičmene moždine. Konverzija M1 u M0 beleži se u 8 (72,7%) tretiranih, a petogodišnje preživljavanje u 9 (81,8%).
Višenedeljna subkutana primena Sandostatina, rezultuje apoptozom malignih ćelija meduloblastoma i potpunom involucijom drop metastaza meduloblastoma u većine pacijenata. In loco primena Sandostatina kombinovana sa protrahovanom subkutanom depo aplikacijom, može značajno suprimirati rast meduloblastoma.

Ključne reči: *Visokorizični meduloblastom, sandostatin, intrakavitarna i subkutana terapija, drop metastaze*