ROLE OF SINGLE USING OF METRONIDAZOLE IN COMBINATION WITH STEREOTACTIC RADIOSURGERY IN THE TREATMENT OF BRAIN METASTASES

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Abstract
The authors first investigated a single using of metronidazole as radiosensitizer in addition to stereotactic radiosurgery (SRS) and its role in the treatment of brain metastases. The results obtained on first 7, 14 and 21 days indicated a high efficiency of the combination of single using of metronidazole and SRS and also demonstrated rapid reduction of tumor volume and elimination of signs of mass effect, in comparison with partial surgical resection.

Keywords: stereotactic radiosurgery, metronidazole, brain metastases

Introduction
The therapeutic effect of LINAC-radiotherapy for irradiation of relative large tumors over a few centimeters in diameter, declines to one-third for small tumors because of the presence of many hypoxic tumor cells and the abundance of the antioxidant enzymes, including peroxidase, and catalase [1]. This is because about two-thirds of the therapeutic effect of LINAC is associated with an indirect influence of X-rays and/or hydroxyl radicals on the electrons in the cytoplasm and intracellular molecules of water [1]. Thus, with the absence of oxygen in tumor tissue, the effect of X-rays and electrons declines to one-third of the standard efficiency.

So called bioreductive agents are substances which are recovered by "biological" ferments to active and toxic metabolites. The chemical nature of these compounds is that their metabolism is most active in the absence of oxygen, they are selective to the anaerobic tumor tissues, which is the basis of using them as radiosensitizers [1,2]. Metronidazole is one of such radiosensitizers, which generates reactive oxygen species by disintegration in anaerobic tumor cells [2].
In the world literature there are not many articles devoted to radiotherapy of brain metastases using metronidazole [3, 4, 5, 6]. Nevertheless, in 1994, Acharya DK. Published a retrospective analysis of radiotherapy in combination with metronidazole in the treatment of 717 patients with various forms of cancer. Metronidazole was used at a dosage of 2g, 4 hours prior to the radiotherapy session, for 5 days in a total of 6-7 weeks. The results of the study observed a positive response of tumors to radiotherapy with metronidazole [3]. In contrast, other studies (Aiken R, Leavengood JM, Kim JH et al. 1984.) reported using of metronidazole only during the whole brain radiotherapy (WBRT) for brain metastases and noted that on the one hand, the combination WBRT with taking metronidazole did not affect the median survival nor the local and distance control of tumor growth, but on the other hand causes a number of side effects, including nausea and vomiting, for which 10 % of patients abandoned metronidazole treatment [4]. This was also confirmed by the randomized study by Eyre HJ, Ohlsen JD, Frank J at all, 1984., where in the group using only WBRT, median survival was 14 weeks, whereas in the group using WBRT + metronidazole, only – 12 [5], and the later study in 2009 by Gustavo AV, Gustavo BM, Ellen C., at all, for example, in which were studied prognostic factors influencing median survival, local and distance control of tumor growth at WBRT and WBRT + radiosensitizers (including metronidazole ) for a large group of patients (2013 patients with brain metastases ) and there were no significant differences in the group using radiosensitizers except motexafin [6], the study of the therapeutic action of which in combination with WBRT was conducted in other studies during the treatment of multiple metastases with emphasis on neurocognitive functions in the course of treatment. Further scientific works using metronidazole in combination with radiotherapy were not found appropriate [6, 7].

But in the world literature there is no data on the single session metranidazol to enhance the effect of stereotactic surgery. Therefore, in our study, we sought to determine what is the role of a single application of metronidazole as radiosensitizer in combination with single session stereotactic radiosurgery.

**Investigation methods**

In January and February 2014 at our institution, stereotactic radiosurgery in combination with metronidazole (SRS + M) was performed for 8 patients, who have taken 2g of metronidazole orally 4 hours prior the radiosurgery session. Five patients had a primary non-small cell cancer of the lung (NSCCL), two – breast cancer and one – melanoma. Patients were 5 men and 3 women. Average age was 53 years (range 36 to 70 years). In three cases there was a single (solitary) metastasis, 2 – single (3 metastasis) and 3 – multiple metastases (6 to 8 lesion).

Each patient was observed for 3 weeks, every 7 days. With a little tolerance in 3 cases (2–3 days). Control was carried out by MRI. MRI data before and after radiosurgery+metronidazole (SRS+M) was compared. The linear dimensions and volume of the metastasis were measured, as well as the percentage of reduction of tumor volume from the initial volume.

Treatment was carried out on the Linac unit. Patients underwent the fixation of a stereotactic frame, or the imposition of a «BrainLAB» thermoplastic mask and the topographometric multi-layer spiral CT preparation using «BrainLAB» localizer. Planning was carried out on «iPlan» workstation using MRI and CT data. The technique of IMRT + Dyn Arc was used. 4 hours prior to the SRS patients took 4 capsules (dose of 500mg) of metronidazole orally with a total dose of 2g. All patients underwent the treatment well.

**Research results**

The most significant changes on MRI were observed already during the first 7 days in two patients with brain metastases from non-small cell lung cancer (NSCLC). Moreover, one patient’s metastasis volume decreased by more than 7cm$^3$ in first 7 days, representing 27% of the initial volume (Figure 1), 10cm$^3$ in 14
days (Figure 2), and 14 cm$^3$ in 21 days, which means more than 50 % of its original volume (Figure 3). Another one patient with a solitary metastasis from NSCLC tumor volume decreased by 3 cm$^3$ 7 days after SRS + M, which is 32 % of the initial volume of metastasis (Figure 4) and another ones– to 2,587 cm$^3$, which is 20 % of the initial volume (Figure 5). In a patient with metastatic melanoma, tumor volume decreased by 4 cm$^3$ in the first 7 days, representing 25 % of the initial tumor volume (Figure 6). The patient with metastatic breast cancer (number 3), reduction of lesion after SRS + M was observed every subsequently every 7 days, in 21 days its volume decreased by more than 50%, the area of edema was completely reduced (Figure 7 and 8). The patient with metastatic NSCLC (number 6) had a tumor volume shrinkage (decreasing sizes of metastases), on the average 46.1% (Table 1) including some of them more than 50 % in 10 days after SRS + M (Figure 9).

Table 1. Changing of MRI data for 6 metastases in patients with NSCLC after 10 days of SRS + M

<table>
<thead>
<tr>
<th>№ tumor</th>
<th>Volume of lesion before SRS + M (cm$^3$) and dose (Gy)</th>
<th>Volume of lesion 10 days after SRS + M (cm$^3$)</th>
<th>Tumor volume shrinkage (in percent)</th>
<th>Reduction of area of peritumoral edema (percentage)</th>
<th>The reduction of the signs of mass effect (max. ++ +)</th>
<th>Reducing the enhancement of contrast (max. + + +)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor 1</td>
<td>0.043 (12.5)</td>
<td>0.017</td>
<td>60</td>
<td>96</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Tumor 2</td>
<td>3.588 (12)</td>
<td>2.305</td>
<td>36</td>
<td>44</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Tumor 3</td>
<td>0.999 (12)</td>
<td>0.505</td>
<td>49</td>
<td>100</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Tumor 4</td>
<td>0.250 (12)</td>
<td>0.117</td>
<td>53</td>
<td>86</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Tumor 5</td>
<td>11.389 (11)</td>
<td>8.781</td>
<td>23</td>
<td>70</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Tumor 6</td>
<td>0.925 (12)</td>
<td>0.407</td>
<td>56</td>
<td>100</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Average value</td>
<td>2.865 (12Gy)</td>
<td>2.022</td>
<td>46.1</td>
<td>82.6</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

The patients didn’t have any decline in neurological status. All patients demonstrated improvement of neurological status during the first 7 days. Among the side effects after taking metronidazole there was a hiccups on 2 and 3 days after SRS + M.
Figure 1. Patient 52 years old, with a solitary NSCLC metastasis in left hemisphere of the cerebellum. MRI before (A) and 7 days after SRS+M (B). Tumor volume decreased by 27%, reduced area of peritumoral edema.

Figure 2. The same patient. MRI before (A) and 14 days after SRS M + (B)
Figure 3. The same patient. MRI data before (A) and 21 days after the SRS + M (B). 26,200 cm$^3$ volume of metastasis in general decreased to 12 cm$^3$ (more than 14 cm$^3$ in 21 days).

Figure 4. 53 years old patient, NSCLC. Solitary metastasis in the left posterior-temporal-occipital region. MRI before SRS+ M (A) and 7 days after (B). Volume of metastasis decreased from 8 cm$^3$ to 5 cm$^3$ (3 cm$^3$), or 32% of the initial volume. Edema and compression area of the triangle of the left ventricle has significantly reduced. Tumor decreased mainly due to the solid component, with a significant enlarged contrast enhancement.
Figure 5. 55 years old patient with non-small cell lung cancer. Multiple brain metastases (number 8). MRI before SRS (A) and 7 days after the SRS+M. In 7 days the volume of metastasis in the left parietal lobe decreased to $2,587 \text{ cm}^3$, the degree of contrast enhancement and the area of edema decreased.

Figure 6. 35 years old patient. Melanoma solitary metastasis. MRI data before (A) and 7 days after SRS + M (B). Metastasis volume decreased by $4\text{ cm}^3$. 
Figure 7. A 40 years old woman with multiple metastatic breast cancer. MRI data before (A) and 7 days (B), 14 days (C) and 21 days after the SRS + M (G.) Lesion volume decreased significantly. Area of edema reduced in 7 days.
Figure 8. Same patient. Metastasis of the left frontal lobe. MRI data before (A) and 7 days (B), 14 days (B) and 21 days after SRS + M (T). Lesion volume decreased significantly (by more than 50%). Zone of edema completely reduced in 21 days.

Figure 9. 50 years old patient. NSCLC (condition after 6 courses of chemotherapy and radiotherapy). Multiple brain metastases (number 6). MRI before (A) and 10 days after (B) SRS + M. The volume of lesion at the bottom left-parietal region decreased by more than 50%. Zone of edema reduced. Signs of mass effect absent. The significant improvement of neurological status of the patient was observed. The remaining lesions also decreased on average by 46.1%.
Discussion

Since we did not find similar works in the world literature on a single application of metronidazole (MTZ) for single session stereotactic radiosurgery in the treatment of brain metastases, we determined the dosage of the drug according to the works on the application of metronidazole during WBRT for brain metastasis [3,4,5,6]. That is why it was decided to use a dose of 2g. The first patient was a patient with non-small cell lung cancer (NSCLC).

Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths and the most common source of brain metastases. It is estimated that 30 to 50% of lung cancer patients undergo metastasis in the brain in the course of illness [8]. Patients with NSCLC brain metastases without treatment have median survival of 4 weeks and almost all die due to intracranial progression is a process, not because of the development of primary tumors [9]. Management and treatment of metastatic brain tumors are complex and depend on several factors, including age, Karnofsky Performance Status (KPS), number of metastases and primary tumor local control. Treatment options for metastatic NSCLC can be: WBRT and stereotactic radiosurgery (SRS) [10]. However, several randomized studies have shown an adverse effect of WBRT on neurocognitive function which, in turn, correlates with decreased quality of life [8, 9, 10]. In contrast, SRS provides great advantages in the control of local tumor growth, with insignificant risk of neurological disorders [10, 11].

The only problem during conducting the SRS is a decision on the dose selection for larger metastases [12].

We took into account the experience of their colleagues and the data of world literature, and recommended protocols RTOG for tumors larger than 3cm. Therefore, during the treatment of the first patient, based on the size of metastasis (more 26cm³) and localization process in posterior fossa, near brainstem, we restricted the prescribed dose to 12Gy [13], and in two cases with multiple metastases (number 8) according the prescribed dose of radiosurgical treatment of multiple metastases [14].

Moreover, given the evidence in the literature, that a number of radiosensitizers (eg metronidazole), increase the effectiveness of radiation therapy of malignant tumors, by O2 saturation, we decided to use a one-off single session of metronidazole during SRS to determine the effectiveness of its role as a radiosensitizer.

Surprisingly after SRS + M the first patient had an effect of the rapid (fast) decrease in tumor volume in 7 days. Further follow-up showed a reduction of metastasis in 14 days by another 3cm³. While we have identified a decrease of metastasis by 10cm³ in 14 days the structure of metastasis and its form left almost unchanged, and the diffusion coefficient of performance (ADC) decreased from 1.2 to 1.0, apparently due to compaction of tumor cells. Reduction in tumor volume happened due to the necrotic area in the center of the lesion. We observed the effect that best to be encompassed by the term "tumor shrinkage". And most likely it was due to the action of metronidazole on tumor cells but not the actual impact of radiosurgery, the effect of which we expected not earlier than 4-6 weeks after the SRS. Nevertheless, it is a significant decrease in tumor volume and reducing the total area of edema already in 7 days, completely eliminated the effect of mass signs which might lead to obstructive hydrocephalus, and threatened the life of the patient.

Further observations, however, showed that the size of NSCLC metastases decreases due to the solid component of the tumor. So in another patient with a decrease in tumor volume by 32% in 7 days it happened due to solid peripheral portion of the tumor, the intensity of its radiographic opacification decreased almost twice. Careful attention was paid to the perifocal edema zone, signs of mass effect and the degree of contrast enhancement of the tumor. And in most cases we observed the complete or partial reducing of edema zone and mass effect characteristics, with an intense decrease of contrast enhancement in 7 days after SRS + M.
The results of a rapid response of NSCLC metastasis to SRS + M, have led us to use the SRS + M for radioresistant melanoma brain metastases and radiosensitive breast cancer metastases, which also led to positive results of the treatment, such a rapid response to SRS + M.

Thus, in our observations, single using of metronidazole as a radiosensitizer during stereotactic radiosurgery (SRS + M) for brain metastases, we found significant efficacy in the treatment of NSCLC, melanoma and breast cancer. It's worth noting that we have considered the observation period of the first 3 weeks (till usually expected result of SRS without metronidazole appear, in 4-6 weeks), with the purpose to observe the rapid response to treatment and eliminate the signs of mass effect, which are threatening the life of the patient. At the same time, we continue to monitor patients with the purpose of local and (distance) remote control of tumor growth, with subsequent determination of median survival. Our plans also include conducting SRS + M for patients with brain metastases from other primary tumors.

Conclusion
Single using of metronidazole as radiosensitizer during single session stereotactic radiosurgery significantly increases the effectiveness of treatment of brain metastases, with a rapid response to treatment, such as a reduction in tumor volume, area of perifocal edema and eliminating signs of mass effect, comparable to the partial surgical resection.

Reference

