ELECTRONICS AND ELECTRICAL ENGINEERING
ISSN 1392-1215 *2006. Nr. 4(68)*
ELEKTRONIKA IR ELEKTROTECHNIKA

MEDICAL TECHNOLOGY
T115
MEDICINOS TECHNOLOGIJA

Radiosensitized Treatment of Primary or Metastatical Malignant Brain Tumors with Hematoporphyrin Derivative

L. Bloznelytė-Plėšnienė, L. Rutkovskienė
Laboratory of Laser and Photodynamic Treatment, Institute of Oncology, Vilnius University,
Santariskiu str. 1, LT-08406 Vilnius, Lithuania, phone: +370 5 2786805; fax: +370 5 2720164; e-mail: pdt@mail.lt

Introduction

Human brain is not tolerant to amounts of gamma radiation up to 60 Gy that are typically used by traditional oncological radiation therapy. This amount can be considerably reduced if the gamma radiation is applied to malignant tumors sensibilized by a derivative of hematoporphyrin (HpD) Several important questions arise concerning this methodology : what is the optimal wavelength of ionizing radiation. What is an effective regime and dosage of radiation. Answers to these questions depend on the morphological type of the tumor. In the present study we refer to the results of the treatment of 48 patients with malignant brain tumors.

Photodynamic therapy (PDT) is a binary treatment modality suitable for various malignant tumors including brain cases. It depends on the selective uptake and retention of a photosensitizer by tumor tissue followed by irradiation of the tissue with the light of an appropriate wavelength. This light activates the sensitizer, and it causes selective destruction of the tumor. Tumor selectivity for HpD has been demonstrated in various experimental and human tumors. A study of biopsy material in patients undergoing PDT for cerebral glioma in the Royal Melbourne Hospital [1] showed that HpD was selectively localized in all grades of glioma. The levels were highest in glioblastoma multiforme (HpD tumor: brain ratio of 30:1) and lower in astrocytoma (8:1). High level of porphyrins has been noticed in glioma tissue, therefore sensitized gliomas treatment is hopeful. On the other hand, the depth of visible light penetration is limited. Our hypothesis was that some of the rays which can provide ionizing radiation (x-rays and/or gamma rays) could activate some of HP derivatives. A publication by Zhao F.Y.[2] featuring the favourable effect of concomitant PDT on the results of gammatherapy prompted us to raise this hypothesis. To prove it, we have performed experiments on more than 1000 mice and rats [3]. The aim of this experimental work was to investigate and enlarge the possibilities of sensitized malignant tumor treatment using some derivatives of hematoporphyrin as a radiosensitizer. Our first experimental experience on radiosensitized treatment, using some derivatives of hematoporphyrin as a radiosensitizer, was published in 1987 [4]. Favourable results of our animal experimental study has encouraged us to utilize radiosensitized treatment (RST) in the clinic of Lithuanian Oncology Centre in 1989 [5]. Since 1989 the total of 238 patients have undergone RST [5, 6, 7]. The radiosensitized treatment has been especially effective in malignant brain tumors [8].

We applied RST only to the patients who, either because of the location of the tumor, its histological shape or outspread could not undergo any other usual radical treatment: surgery, radiation or chemotherapy, or the possibilities of such treatment were already exhausted.

Our clinical research: "Radiosensitized treatment of malignant brain tumors (gammadynamic treatment). Investigation of effectiveness and safety" was approved by Lithuanian Bioethics Committee.

The purpose of this paper is to review our results of the radiosensitized treatment of primary and metastatical malignant brain tumors.

Material and methods

Clinical characteristics of the patient. From March 1998 to July 2003 the total of 48 patients with malignant brain tumors underwent radiosensitized tumors treatment as palliation. There was no possibility of radical treatment for all these patients. There were 38 patients with primary malignant brain tumors, 4 patients with solitary metastatic brain tumors and 6 patients with tumors grown into the brain from the surrounding tissue. Computed tomography (CT) and/or magnetic resonance imaging (MRI) examination was provided for all of them before the treatment and 1 or 1.5 mo. after each RST course. At the point, when the full tumor's regression was established, the CT and/or MRI examination was provided twice a year. The histological verification was provided in 46 cases (in 38 cases it was provided after the tumor's resection in 7 cases it was provided after the tumor's biopsy and in one case after the autopsy). In two cases it was impossible due to the tumor's localization. Among 38

patients with primary malignant brain tumors the histological examination revealed glioblastoma in 15 patients (in one case glioblastoma was estimated after the autopsy - 3 years later after the beginning of the treatment, the patient was refered to as patient with astrocytoma); astrocytoma anaplasticum in 9 patients; astrocytoma in 3; ependymoma anaplasticum in 3; chordoma in 2 patients; meduloblastoma in 1; neuroblastoma in 1; oligodendroglioma in 1; and germinoma in 1 patient. In the rest two cases the tumors histology was unknown. These two tumors were primary. Among 4 patients with metastatical malignant brain tumors, the histological examination revealed the following situation: melanoma in 1 patient and adenocarcinoma in 3 patients. Among 6 patients with tumors grown into the brain from the surrounding tissue, histological examination revealed melanoma in 1 patient; chondrosarcoma in 1 patient; mucoepidermoid carcinoma (from parotid gland) in 1 patient and adenoid cystic carcinoma in 3 patients. Among 48 patients with advanced primary or metastatical brain tumors, there were 6 previously untreated cases (2 with primary brain tumors; 3 with metastatical brain tumors; 1 with tumor which was grown into the brain from the surrounding tissue). The rest 42 before RST had undergone radiotherapy (38 patients), surgery (31 patient) and/or chemotherapy (10 patients). At the start of the treatment, the condition of most patients (22) was serious. The condition of 17 patients was critical. Karnofsky performance scale index was estimated for all the patients at the beginning of the treatment, immediately after it, and finally two weeks later. At the beginning of the treatment it was only 10% in 14 patients, 20% in 9 patients, 30% in 11 patients, 40% in 4 patients, 50% in 3 patients, 60% in 5 patients and 90% in 1 patient. Figure 1 presents Karnofsky performance scale index for these patients until RST and two weeks after RST.

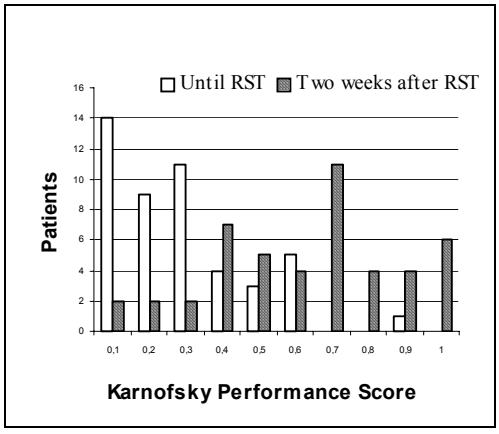

Fig. 1. Karnofsky performance scale index for 48 patients with malignant brain tumors treated by us before RST and 2 weeks after RST

Procedures

During the radiosensitized treatment hematoporphyrin derivative (HpD) was injected i.v. The dose was 5 mg/kg body weight. HpD was dissolved in 500 ml 0.9% sol. natrii chloridi. 24, 48 and 72 h after the injection of the sensitizer, tumors were irradiated with gamma rays 2 Gy at a time from radioactive 60Co (the full dose of the course was 6 Gy). The duration of the treatment was 4 days. Providing RST the additional medicamental treatment was applied to most patients: i/m injections of dexamethasone (usually 4 mgx2) and i/v injections of mannitoli 10%-500 ml. As the derivatives of hematoporphyrin sensitize skin to the sunlight, precautions were taken not to expose the patient to the direct sunlight, or to any blazing light, ultraviolet light in particular. Since HpD injection, the patients were restricted to darkened rooms for two weeks. 12 patients underwent one course of the treatment. For the rest the treatment was repeated after 1-12 months (mo). 6 patients underwent two courses, 9 patients - 3 courses, 4 patients - 4 courses, 6 patients - 5 courses, 6 patients - 6 courses, 1 patient - 7 courses, 1 patient - 8 courses, 3 patients - 9 courses. All the patients were followed up for the period of 3 mo. to 63 mo., except 5 patients who died 0.5-2 mo. after RST. The median follow up lasted 12 .9 mo..

Statistics

Statistical analysis was carried out using the SAS system soft-ware program. Kaplan-Meier survival analysis was used to obtain median survival rates for (a) all patients with malignant brain tumors; (b) only for the patients with malignant gliomas; (c) only for the patients with astrocytoblastomas and glioblastomas; (d) only for the patients with glioblastomas. For comparison of the median survival rates among patients for whom RST was provided (a; b; c; d groups), and analogical patients for whom usual treatment was provided with the best results we had found in the available literature. Signed rank test was used. A p value of ≤ 0.05 was regarded as statistically significant.

Results and discussion

The primary result was already noticeable during the treatment. An especially rapid effect was observed in the 17 patients who had been in a critical condition. 5 of 7 patients who had been in a coma (1 to 8 weeks before RST) came into contact on the third day of the treatment. 3 of the 7 patients began to walk, speak and even read within two weeks. Nausea disappeared in 8 patients immediately after RST. In 2 out of 4 patients the sounds were removed as their swallow normalized. Overall, 33 out of 48 patients experienced a significant improvement. For 10 patients the improvement was not so evident, and for 5 patients the effectiveness of RST was slight or RST was ineffective. Karnofsky performance scale index increased immediately after RST in 33 patients (Fig. 1). Two weeks after the first RST course, it was 10% only in 2 patients, 20% in 2 patients, 30% in 2 patients, 40% in 7 patients, 50% in 5 patients, 60% in 4 patients, 70% in 11 patients, 80% in 4 patients, 90% in 4 patients and 100% in 6 patients. The notably rapid improvement of the state of health was established within the first two weeks in most patients. Later on, the stabilization of the state of health was noticed. The duration of such stabilisation varied from 2 to 6 weeks, depending on the morphologic type of the tumor. The duration of such stabilisation in glioblastomas multiformes usually lasted 1 or 2 weeks, in

astrocytoblastomas – 1 to 3 weeks in low-grade astrocytomas – 1 to 6 mo. in ependymomas malignum – 1 to 4 mo. The tumors of different histogenesis require some RST modifications. It was estimated during our experiments with rats and mice and our clinical experience proved it. In 4 patients all malignant brain tumors fully disappeared after a single RST course. In all these cases the diameter of the tumors was less than 3 cm. If there was no full regression of the tumor, the first symptoms of the recurrence of the disease usually appeared in 1 or 2 mo. after RST. Then the treatment was repeated. CT and /or MRI examinations, which were provided 3 or 6 weeks after RST, revealed the regression of tumor in 34 patients. As a result of the radiosensitized treatment of malignant brain tumors, 11 malignances (in 9 patients) fully disappeared after a single RST course (in 4 patients) or after some RST courses (in 5 patients). However the recurrent disease was noticed in two patients after 24 mo. (glioblastoma) and 6 mo. (glioblastoma). A significant response – regression of more than 75% of the tumor and the remission of the disease for over 6 mo. was established in 17 patients with malignant brain tumors. A partial response was noticed in 17 patients with malignant brain tumors. For the rest 5 patients the treatment was ineffective. The median survival of patients with malignant brain tumors treated by the addition of RST was 28 mo. The median survival of patients with glioblastoma (14 patients) treated by the addition of RST was 21 mo. At present 15 of these patients, who have undergone RST, are alive and well. 7 of them have been without brain tumors for 39 mo., 28 mo., 18 mo., 16 mo., 15 mo., 15 mo., and 13 mo. after RST treatment.

The median survival of 48 patients with malignant brain tumors treated by the addition of RST, was 28 mo. (Fig. 2A), whereas at present, the best available treatment for malignant brain tumors results in median survival of patients for 15 months despite surgery, radiotherapy, and chemotherapy [9]. The median survival of patients treated by the addition of RST with malignant gliomas (glioblastoma and anaplastic astrocytoma – 21 patient) was 23mo. (Fig.2B). Comparing it with the 10.4 mo. (n =84) or 12 mo., and even 14.5 mo. (n=48), documented in the literature, the median survival of such patients was statistically significant ($p<0.005$) [10, 11, 12, 13]. The median survival of patients treated by the addition of RST with glioblastoma (14 patients) was 22 mo.(Fig.2C).Comparing it with the 13.8 mo, median survival of such patients (n=58)[14] was statistically significant ($p < 0.005$).The median survival of patients with primary malignant brain tumors (39 patients) treated by the addition of RST was 27 mo.

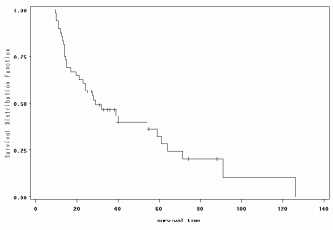

Fig. 2A. Kaplan-Meier survival curve (in mo.) for patients with malignant brain tumors treated by the addition of RST

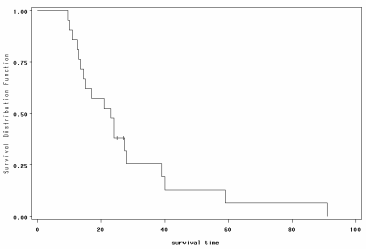

Fig. 2B. Kaplan-Meier survival curve (in mo.) for patients with malignant gliomas treated by the addition of RST

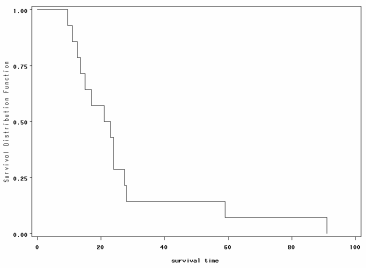

Fig. 2C. Kaplan-Meier survival curve (in mo.) for patients with glioblastoma treated by the addition of RST

Adverse effects of the treatment were minimal. All the patients were warned to wear protective clothing and to use sunscreen preparations if they were exposed to sunlight at least for one month. However well marked skin hyperpigmentation was noticed in 8 out of 48 patients treated by us.

While primary malignant brain tumors account for only 2% of all adult cancers, these neoplasms cause a high amount of cancer – related deaths. In spite of the advance in surgery, radiation therapy and chemotherapy, the persentage of the prognosis for primary malignant brain tumors remains very low. Less than 10% of all patients with malignant brain tumors survive 2 years, and less than 5% live up to 5 years [10]. The incidence of primary brain tumors is increasing. Malignant gliomas (glioblastoma and anaplastic astrocytoma) are the most common primary brain tumor in adults, occurring at a rate of 5-8 cases per 100000 population per year. Clinical data from 1491 patients harboring a glioblastoma multiforme that has been diagnosed between 1988 and 1998 at the University of California at San Francisco neurooncology clinic were retrospectively reviewed by Pasra et all. The median survival time in such patients was 9.8 mo. [15]. It is important to point out that survival in glioblastoma cases has not changed significantly over the past three decades, so the emergence of novel treatment methods for these tumors has led to a heightened interest.

Conclusions

Radiosensitized treatment, using the derivatives of hematoporphyrin, is a new and effective method of the treatment of malignant brain tumors both: primary and metastatical. The effectiveness of this treatment depends on the morphological type of the tumor. The best effect was noticed in patients with astrocytoblastoma, ependymoma malignum and in patients with solitary

metastatic brain tumors when primary tumors were adenocarcinomas or adenocystic carcinomas. The tumors of different histogenesis require some RST modifications.

References

1. **Popovic E. A., Kaye A. H., Hill J. S.** Photodynamic therapy of brain tumors // Semin Surg Oncol. – 1995. – Vol.11. – P. 335–45.
2. **Zhao F. Y., Zhang K. H., Huang H. N,. Sun K. H., Ling Q. B., Xu B.** Use of haematoporphyrin derivate as a sensitizer for radiotherapy of oral and maxillofacial tumours: preliminary // Lasers Med Sci. – 1986. – Vol. 1. – P. 253–6.
3. **Bloznelyte L., Giniunas L., Didziapetriene J**. Action in vivo hematoporphyrin derivative, excitated by ionizing radiation // International Conference of Photodynamic Therapy, Sofia October 3-5, 1989.
4. **Блознялите Л., Шлякис Г.** Применение гематопорфириновых дериватов вместе с лазерным воздействием и телегаммaтерапией для лечения прививаемых злокачественных опухолей // Усовершенствование и интеграция современных методов лучевой диагностики. – Вильнюс, 1987. – Ч. 2. – С. 289 – 290.
5. **Блознялите Л.** К вопросу о фотодинамической и гаммадинамической терапии в онкологии: Автореферат диссертации на соискание ученой степени кандидата медицинских наук. – Вильнюс, 1990. – 23 с.
6. **Bloznelyte L., Stancius A.** Sensitized tumor therapy // Acta Med Lituanika. – 1994. – Vol. 1. – P. 51–4.
7. **Bloznelytė-Plėšnienė L**. Photodynamic treatment in Oncology Practice. Thesis for a degree of habil. doctor of medicine. - Vilnius, 1997. – 34 p.
8. **Bloznelytė-Plėšnienė L**. Radiosensitized treatment of malignant brain tumours // Lasers Med Sci. – 2002. – Vol. 4. – A27.
9. **Kostron H, Obwegeser A, Jakober R.** Photodynamic therapy in neurosurgery: a review // J Photochem Photobiol B: Biol. – 1996.. – Vol. 36. – P. 157–68.
10. **Azizi S. A., Miyamoto C.** Principles of treatment of malignant gliomas in adults: An overview // J NeuroVirol, 1998. – Vol. 4. – P. 204-16.
11. **Laperriere N, Zuraw L, Cairncross G**. Radiotherapy for newly diagnosed malignant glioma in adults: A systematic review // Radiother Oncol. – 2002. – Vol. 64. – P. 259–73.
12. **Behin A, Hoang-Xuan K, Carpentier A. F., Delattre J. Y.** Primary brain tumours in adults // Lancet. – 2003. – Vol. 361. – P. 323-31.
13. **DeAngelis L. M.** Brain tumors // N Engl J Med. – 2001. – 2: 114–23.
14. **Brandes A. A., Lacombe D, Vecht C**. Future trends in the treatment of brain tumours // Eur J Cancer. – 2001. – Vol. 37. – P. 2297–301.
15. **Parsa A. T., Wachhorst S., Lamborn K. R.** et al. Prognostic significance of intercranial dissemination of glioblastoma multiforme in adults // J. Neurosurg. – 2005.– V. 102-622-628.

Presented for publication 2006 02 10

L. Bloznelytė-Plėšnienė, L. Rutkovskiene. Radiosensitized Treatment of Primary or Metastatical Malignant Brain Tumors with Hematoporphyrin Derivative // Electronics and Electrical Engineering.- Kaunas: Technologija, 2006. – No. 4(68). – P. 83–86.

Human brain is not tolerant to amounts of gamma radiation up to 60 Gy that are typically used by traditional oncological radiation therapy. This amount can be considerably reduced if the gamma radiation is applied to malignant tumors sensibilized by a derivative of hematoporphyrin (HpD) Several important questions arise concerning this methodology: what is the optimal wavelength of ionizing radiation. What is an effective regime and dosage of radiation. Answers to these questions depend on the morphological type of the tumor. In the present study we refer to the results of the treatment of 48 patients with malignant brain tumors. Ill. 4, bibl. 15 (in English; summaries in English, Russian and Lithuanian).

Л. Блознелите-Плэшнене, Л. Рутковскене. Лечение первичных злокачественных опухолей мозга и метастазов в мозгу радиосенсибилизированных произиодными гематопорфирина // Электроника и электротехника. – Каунас: Технология, 2006. – № 4(68). – С. 83–86.

Представлены данные радиосенсибилизированной терапии первичных злокачественных опухолей мозга и метастазов в мозгу злокачественных опухолей других органов. Лечено 48 болъных. Через 24, 48 и 72 часов после введения радиосенсибилизатора произиодного гематопорфирина опухоли подверглись гамма облучению 2 Gy. У 9 болъных после 1 или нескольких курсов радиосенсибилизированной терапии опухоли полностью исчезли, хотя у 2 из них возникли рецидивы через 24 и через 6 месяцев. Регресия опухоли и ремиссия болезни, которая длилась 6 месяцев и дольше, имела место у 17 болъных Кратковременная ремиссия (от 2 до 6 месяцев) была у 17 больных. У 5 больных лечение было не эффективно. Данные работы приводят к заключению, что радиосенсибилизированная терапия являетса новым эффективным методом лечения опухолей мозга. Эффективность радиосенсибилизированной терапии зависит от морфологического типа опухоли. Ил. 4, библ. 15 (на английском языке; рефераты на английском, русском и литовском яз.).

L. Bloznelytė-Plėšnienė, L. Rutkovskienė. Hematoporfirino dariniais radiosensibilizuotų pirminių smegenų navikų ir metastazių smegenyse gydymas // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2006.- Nr. 4(68). – P. 83–86.

Šio darbo tikslas buvo ištirti sensibilizuotų navikų terapijos galimybes naudojant hematoporfirino darinį (HpD) kaip radiosensibilizatorių. Radiosensibilizuotų navikų terapija (RST) taikyta gydant 48 ligonių pirminius piktybinius smegenų navikus ar kitų navikų metastazes smegenyse. Praėjus 24, 48 ir 72 val. po HpD injekcijos (i/v) navikai švitinti 2 Gy. Po vieno ar kelių RST kursų 9 pacientams navikai visiškai išnyko, tačiau dviem iš jų atitinkamai po 24 ir po 6 mėn. atsirado recidyvai. Navikų regresija ir ligos remisija trunkanti 6 mėn. ir daugiau, pasireiškė 17 pacientų. Trumpalaikė ligos remisija, trunkanti nuo 2 iki 6 mėn., pasireiškė kitiems 17 ligonių. Neefektyvus buvo tiktai 5 ligonių gydimas. Iš šio darbo duomenų darome išvadą, kad RST yra naujas ir efektyvus smegenų navikų gydymo metodas. RST efektyvumas priklauso nuo naviko morfologinio tipo. Il. 4, bibl. 15 (anglų kalba; santraukos anglų, rusų ir lietuvių k.).