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TREATMENT OF PROGRESSION OF DIFFUSE ASTROCYTOMA BY HERBAL MEDICINE: CASE REPORT

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Abstract:

Background: The paper presents the results of the use of phytotherapy in a 33-year-old woman who, after finishing the oncological treatment of diffuse astrocytoma, had tumour progression.
Material and methods: Phytotherapy was introduced after the tumour had progressed. It consisted of 4 types of herbal medicine which the subject was taking in form of tea once a day at regular intervals. The patient started phytotherapy along with temozolomide, which was the only oncological treatment she was under after the tumour had progressed. Following the finished chemotherapy, the patient continued the treatment with herbal medicine only. She regularly took phytotherapy without interruption and to the fullest extent for 30 months, and the results of treatment were monitored by periodic scanning using nuclear magnetic resonance technique.
Results: The control scanning that was conducted after the end of combined treatment with temozolomide and phytotherapy showed tumour regression. The patient continued with phytotherapy after finishing chemotherapy and, during the following 24 months, it was the sole treatment option. In that period, the regression of the tumour continued, until a control examination 30 months after the introduction of phytotherapy showed no clinical and radiological signs of tumour.
Conclusion: The results presented in this research paper clearly indicate the potential of phytotherapy in the treatment of some types of brain tumours. A complete regression of tumour following the treatment with nothing but herbal medicine offers support for such claim. Future research should demonstrate the effectiveness of phytotherapy, as a supplementary form of brain tumour treatment, and the results of this research should be compared with the existing information on the effectiveness of the protocols currently used in the treatment of these types of tumour.

Keywords: phytotherapy, diffuse astrocytoma, temozolomide, chemotherapy, nuclear magnetic resonance

Introduction

Diffuse astrocytoma falls into a group of glial tumours, which are most common brain tumours. According to the classification proposed by the World Health Organization (WHO), its degree of differentiation is II (WHO grade II) (Louis et al, 2007). Diffuse astrocytoma is characterized by low mitotic activity, infiltration of surrounding tissue and a high tendency towards malignant progression, leading to the formation of secondary high grade astrocytomas. It can progress gradually from anaplastic astrocytoma (WHO grade III) to grade IV astrocytoma – glioblastoma (GBM), and it is also possible for a direct progression of diffuse astrocytoma into GBM to occur which, on average, takes 4 to 5 years after diagnosis (Ohgaki et al, 1999). After progression, the oncological treatment was administered in accordance with the treatment protocol for high grade glial tumours, which includes surgical removal of the tumour, followed by radiation therapy and chemotherapy with a DNA alkylating agents, usually temozolomide (Stupp et al, 2005).The use of temozolomide (TMZ) in the treatment of brain tumours is limited by the activity of the gene MGMT (O^6-methylguanine-DNA methyltransferase) in tumour cells. This gene encodes an enzyme that effectively repairs the damage caused by TMZ and other alkylating cytostatics, which significantly reduces their effectiveness (Blanc et al, 2004). Studies have shown that the MGMT gene promoter hypermethylation also occurs in primary (36%) and secondary (75%) high grade astrocytomas, which results in the lack of repair of the damage caused by TMZ, and is a positive prognostic factor in the treatment with TMZ, so such patients can expect to benefit from the introduction of the TMZ (Hegi et al, 2005). The survival rate of patients with high grade astrocytoma is low at 3 years for anaplastic astrocytoma and 12-18 months for GBM (Gladson et al, 2010).

The subject of this research paper is the presentation of a case that demonstrates the efficacy of phytotherapy in controlling the growth of diffuse astrocytoma after its progression, and the aim is to present that some pharmacologically active ingredients, which are found in the herbal mixtures, can achieve complete tumour regression.

Case Report

Prior to starting FT, the patient submitted medical records with a diagnosis of treated tumour, set on the basis of the sample of tumour tissue reviewed by a pathologist and a scan of the affected area using computed tomography (CT), as well as all the results of the control examination after the treatment of the primary tumour, concluding with progression. Based on these data, we got an insight into the characteristics and type of the primary tumour, whereas the data that the subject enclosed after the progression were used as a basis for a comparative monitoring of the effectiveness of FT in terms of comparing the dimensions of the tumour before and after herbal medicine was administered.

The paper describes the case of a 33-year-old woman who, due to frequent headaches, epileptic seizures, speech disturbances and stiffness of the right half of the body, in June 2011 at Cantonal Hospital Zenica (Bosnia and Herzegovina) underwent an emergency computed tomography (CT) scanning. The scan showed a well-limited tumour mass without necrosis, located to the left frontotemporoparietally, dimensions: 56 x 45 x 51 mm (**Figure 1A**). In July 2011, the patient underwent surgery, during which a complete resection of the tumour was performed. PH finding showed a diffuse astrocytoma Gr-II. After the surgery, the patient stayed at the radiology ward, where a 3D conformal radiotherapy was performed using a 6MW linear accelerator. The oncology

treatment was completed by administering a therapeutic dose of 54 Gy was administered in 27 fractions. A control scan using nuclear magnetic resonance (NMR) technique, performed in April 2012 (**Figure 1B**), showed the presence of local recurrence, with a diameter of 5 mm, and the scan in September 2012 showed an increase in the tumour to 11 mm (**Figure 1 C**). In February 2013, due to the weakness of the right limbs and speech disturbances, an emergency NMRI was performed, with added contrast (contrast media: gadoteric acid, 0.2 ml/kg), and found the presence of an extensive brain oedema and recurrent tumour, 40 mm in diameter, which was spreading towards the basal ganglia, and a midsagittal plane shifted approximately 9 mm to the right (**Figure 1D**). The patient immediately started with anti-oedema therapy (dexamethasone, 16 mg/day i.v.) and anti-epileptics (Topiramate, 50 mg/2 ×/day and Clobazam, 50 mg/day), and oncology treatment was continued by introduction of TMZ in 6 cycles of 28 days at a dose of 200 mg/m^2 of body surface area, for 5 days during each cycle.

In March 2013, the patient applied for FT and began taking it along with TMZ. A control NMRI performed in October 2013 showed that there had been a regression of the tumour, with the diameter being 22 mm at the time (**Figure 2A**). After 6 cycles of therapy with TMZ, in September 2013, the patient finished the oncology treatment, and further treatment consisted solely of FT. The only pharmaceutical drugs she continued to take were anti-epileptics. Subsequent control scans, performed in February and October 2014, showed a tumour regression (**Figures 2 B and 2C**). Finally, 30 months after the introduction of the FT, the tumour could not be detected on the control scan from 31 August 2015, and the irregular dotted area that post-contrastly raised the signal intensity, was recognized by a physician as a scar of surgery from 2011 (**Figure 2 D**).

The patient was treated with four types of herbal medicines (preparation 1, preparation 2, preparation 3 and preparation 4). Preparations 2 and 4 had been previously used in the treatment of intracranial tumours (Trogrlić et al, 2012). The preparations differ in their composition, and consist exclusively of crushed parts of the plants, without any other additives. The plants included in the composition are pounded to a standard degree. Sieve no. 6 (rough cut) was used for flowers, stems and leaves, sieve no. 3 was used for roots and bark, and sieve no. 2 (fine cut) was used for seeds and fruits (Kovačević, 2000**)**. Herbal medicines are made into tea which patients drink every day at regular intervals. Preparation no. 1 was taken 2 times a day, at 7 a.m. and 7 p.m., while preparations 2, 3 and 4 were taken once a day as follows: preparation no. 2 at 10 a.m., preparation 3 at 1 p.m., and preparation 4 at 4 p.m. All preparations are used in the same manner: to prepare a single dose of tea, 1.5 g of herbal mixture and 200 cm^3 of water is needed.

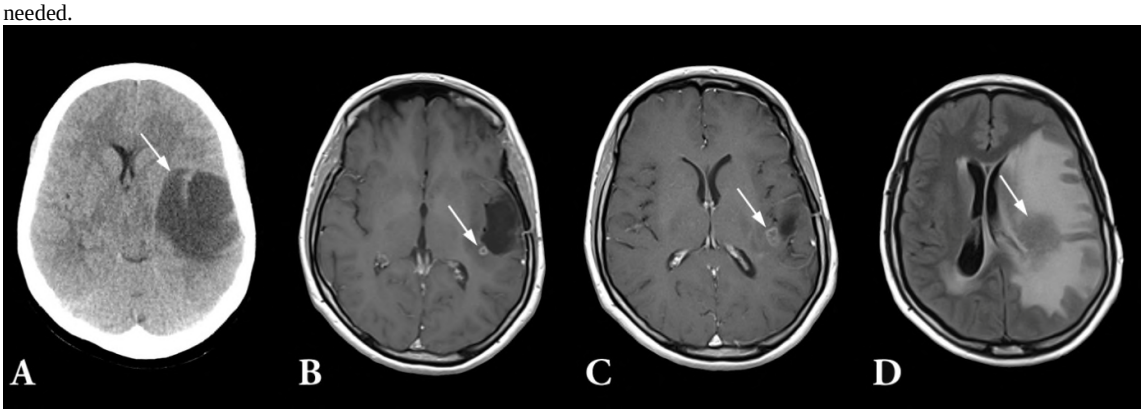

Figure 1: Overview of the control scans prior to the introduction of FT

(A) CT scan of diffuse astrocytoma, (B) NMRI after the completed oncology treatment indicates the 5 mm recurrence, (C) 11 mm recurrence, (D) tumour progression.

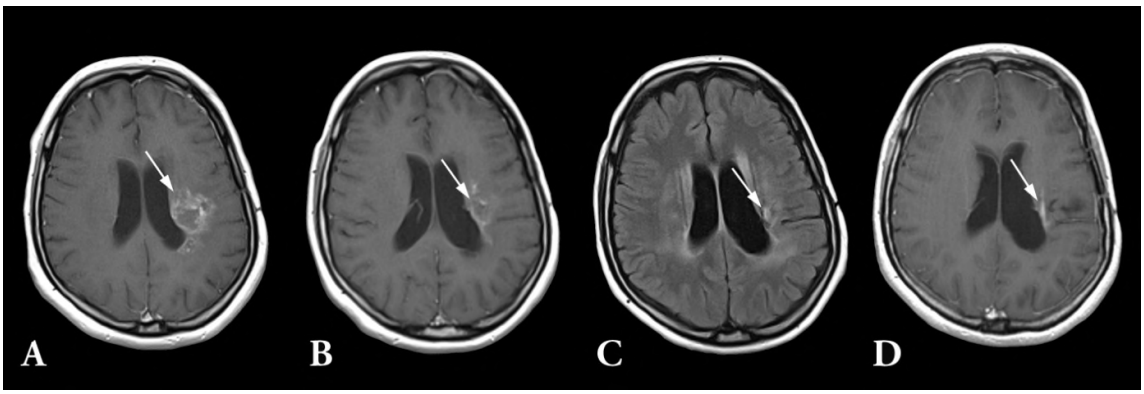

Figure 2: Overview of the control NMRI following the introduction of FT

(A) Control scan upon the completion of the combined treatment with TMZ and FT and the regression of the tumour, (B, C and D) continuation of regression to the point of complete absence of clinical and radiological signs of tumour, achieved only with the FT.

Discussion

This research paper describes a case of a woman who, after malignant progression of previously treated diffuse astrocytoma, started taking FT as a part of her treatment. Although tumour grade was not established, because there had been no surgery nor histological examination of the sample tissue, the indication of the malignant progression (**Figures 1 B and 1C**) was found upon comparison of the control scans from 2012 and scans from February 2013 (**Figure 1D**), which showed a significant increase in the tumour,

accompanied by an extensive oedema which encompassed major portion of the left brain hemisphere. The progression to a higher grade developed quite rapidly, but that was expected, considering the fact that in diffuse astrocytoma an average proliferative index is determined by Ki-67 antibody of approximately 2.5%, whereas the number of dividing cells in this patient was 4-5%, indicating the possibility of faster malignant progression (Okamoto et al, 2004, Peraud et al, 2002**)**. High grade astrocytic tumours, regardless of whether there are primary tumours, occurring *de nove*, or secondary tumours, occurring by a malignant progression of lower grade astrocytoma, are treated by the so-called Stupp-protocol (Stupp et al, 2005). This treatment includes a surgery procedure followed by the combined radiotherapy/chemotherapy (TMZ), and then another 6 cycles of monotherapy with TMZ.

In the case of our patient, physicians came to a conclusion that the surgical procedure imposed a great risk, so they abandoned the idea, and because less than 18 months had passed from the prior radiotherapy treatment, that form of treatment could also not be used after tumour progression. Therefore, the only option left was an introduction of TMZ in 6 cycles of 28 days. The patient started taking FT along with TMZ. Control NMRI performed after the completion of the combined chemotherapy/phytotherapy showed a significant tumour regression. (**Figure 2A**). MGMT promoter hypermethylation status had not been determined, so it was not possible to predict whether the patient would benefit from the introduction of the TMZ (Hegi et al, 2005). Considering the fact that in approximately 75% of secondary high grade astrocytoma MGMT gene promoter hypermethylation was observed, there is a high probability that the patient benefited from the introduction of TMZ, so in terms of tumour regression in the period of the combined chemotherapy/ phytotherapy neither the effect of TMZ nor possible synergistic effect of the two regimens can be excluded. However, further reduction of the tumour to the point when there was no clinical or radiological signs of the disease nor brain oedema can be attributed solely to the activity of pharmacologically active substances from the herbal mixtures. (**Figures 2 B, 2C** and **2D**).

Duration of FT had been determined by the results of control scanning, which was performed for as long as there were any signs of tumour in the patient. In this particular case, FT lasted 30 months. Taking herbal medicine for such a long period entailed the risk of side effects, so the patient was monitored regularly. However, throughout the period she was taking FT, no side effects were observed, which suggests their harmlessness.

It should be noted that, to our knowledge, presented results of the use of FT in the treatment of astrocytic brain tumours, are the first of its kind worldwide. The available literature does not describe similar research, so the obtained results cannot be compared with similar studies in the world. The earlier research papers of the author of this paper did showe that FT can be used in the treatment of macroprolactinoma (Trogrlić et al, 2012), but specific results that would demonstrate the success of the use of FT in the treatment of astrocytic tumours have not been registered in the literature.

Conclusion

In our previous research papers we have already shown that FT has its place in the treatment of intracranial tumours, and this study is a continuation of the research on the potential of FT in the treatment of these types of tumour. The results presented in this research paper are significant, not only because they showed that a complete tumour regression can be reached by using herbal medicines, but also because they determined the direction of future research and pointed to the possibility of introducing FT in the treatment of astrocytic tumours. The authors of this research paper are conducting such research, and the exact composition of the herbal medicine will be published in that report.

Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Abbreviations: CT – computed tomography**; FT** – phytotherapy**; GBM** – glioblastoma multiforme
MGMT - O^6-methylguanine-DNA methyltransferase; **NMRI** - nuclear magnetic resonance; **TMZ** – temozolomide

Competing interests: The authors hereby declare there had been no conflict of interest.

Authors' contributions

IT, DT and ZT participated in the treatment of the patient and analyzed previous published data. DT wrote the manuscript. IT re-edited the manuscript. All authors read and approved the final manuscript.

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