Original Article

ADJUVANT TREATMENT OF BRAIN GLIOBLASTOMA MULTIFORME WITH RABIES VACCINE, DEFEROXAMINE AND D-PENICILLAMINE: A PILOT STUDY

Philip V. Philipov

Clinic of Neurosurgery, Medical University-Pleven, Bulgaria

Summary

Glioblastoma multiforme is the most malignant brain tumor and its treatment is a big therapeutic challenge nowadays. During the recent four years, the author has applied rabies vaccine, Desferal and D-penicillamine (Cuprenil) in adjuvant treatment of twenty patients with brain glioblastoma multiforme. On February 1, 2009, the median postoperative survival of the group was two years and four months. Nine patients were alive. This result is very good, as compared to therapeutic achievements of other authors.

Key words: brain glioblastoma multiforme, adjuvant treatment, rabies vaccine, Desferal, D-penicillamine

Introduction

Glioblastoma multiforme is the most malignant primary brain tumor in adults. Median survival after the operation and radiotherapy (a total dose of 60 Gy) is about 12 months [1-4]. Additional adjuvant means have usually added several months to survival (Table 1) [5-11]. Since 1981, we have used rabies vaccine for adjuvant treatment of 20 patients with brain glioblastomas. The median postoperative survival was 17.2 months [12]. Two decades later, we treated 21 patients with Desferal and Cuprenil (D-penicillamine). The median survival of these cases was 20 months [13]. In this pilot study, we combined rabies vaccine, Desferal and Cuprenil for adjuvant treatment of 20 patients.

Corresponding Author:
Philip Philipov
Clinic of Neurosurgery
University Hospital
8A, G.Kotchev str.
Pleven, 5800
Bulgaria
e-mail: venzirin @ netissat.bg

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Table 1. Postoperative survival of patients with glioblastoma multiforme according to literature data

	Authors	Year	No of patients	Adjuvant therapy	Survival in months
1.	T.Trojanowski et al.	1989	129	CCNU	11.0
2.	P.Kransenek et al.	1990	497	BCNU and vumon 26	12.0
3.	P.Fargeot et al.	1990	19	BCNU	13.0
4.	P.J.Miller et al.	1990	74	-	13.5
5.	R.G.Evans et al.	1990	18	-	15.0
6.	T.Y.D. Pigott et al.	1991	16	-	11.2
7.	C.Davis et al.	1991	9	cisplatine	11.7
8.	K.Nakagawa et al.	1995	9	autologic killer cells	13.5
9.	J.Iwadate et al.	1995	38	ACNU and cisplatine intraarterially	12.5
10.	M.J.Glantz et al.	1996	60	Paclitaxel	9.7
11.	M. Ben-Hassell	1996	206	BCNU	12.0
12.	A.D.Chanana et al.	1999	38	Boron neutron capture therapy	13.0
13.	D.G.Thomas et al.	1999	335	procarbazine, CCNU and vincristine	10.0
14.	M.M.Fitzek et al.	1999	23	accelerated proton/ photon irradiation	20.0
15.	S.Patel et al.	2000	40	I-125 in tumors	11.0
16.	R.G.Selker et al.	2002	137	BCNU	13.5
17.	R.G.Selker	2002	133	BCNU and I-125	14.2
18.	E.C.Nwokedi et al.	2002	33	-	13.0
19.	E.C.Nwokedi et al.	2002	31	gamma knife stereotactic radiosurgery	25.0
20.	R.Stupp et al.	2005	286	-	12.1
21.	R.Stupp et al.	2005	287	temozolomide	14.6

Patients and Methods

Data of the patients treated are on Table 2, compared with the two previous cohorts we studied. The factors, influencing the longer survival in glioblastoma multiforme, besides treatment, are frontal localization of the tumor and younger age of the patients. The relative share of patients with frontal tumors was the same in the three groups. In the present study, we also treated two patients with bifrontal tumours. Patients with such tumor localization are, as a rule, excluded from studies of other authors. These patients deteriorate and die sooner after the operation. The median age of the patients in the present study was 50.1 years. They are older than the patients in our two previous investigations (median age 48 and 43.7 years, respectively).

The weekly medicine intake plan was as follows: one dose of Rabies vaccine on Monday; 0.5g. Desferal® (deferoxamine) intramuscularly on Wednesday, Thursday and Friday; one tablet (capsule) of 250mg. Cuprenil® (D-penicillamine) every day in the morning and in the evening, half an hour before meals. During the first three postoperative years, we strictly applied this regimen. Later, we reduced the treatment to one dose of vaccine and one course of Desferal fortnightly, and one tablet (capsule) Cuprenil daily. We usually started treatment soon after the optimal radiotherapy. In six cases, however, treatment was started in the period of neurological deterioration. When the patients had undergone courses of chemotherapy, our treatment was applied in the free weeks.

Results

On February 1, 2009, the median postoperative survival of the treated patients was 28 months (2 years and 4 months). Nine cases were alive and five of them were in a very good condition. Therefore, this is not final data on survival of the group. The survival for this group was

Table 2. Postoperative survival of our cohort with glioblastoma multiforme

	Sex	Age in years	Localization of the tumor	Volume of the resection	Outcome on 01.02.2009	Survival in months
1.	female	32	bifrontal	partial	alive	59.0
2.	female	63	left frontal	partial	alive	46.0
3.	male	63	left frontal	partial	alive	36.0
4.	female	41	bifrontal	partial	alive	35.0
5.	male	37	right temporal	partial	alive	35.0
6.	male	52	right parietal	partial	alive	33.0
7.	male	32	right temporal	partial	alive	30.0
8.	female	30	right frontal	partial	alive	29.0
9.	female	39	right frontal	partial	alive	12.0
10.	male	74	left frontal	partial	died	36.0
11.	female	58	right frontal	partial	died	34.0
12.	male	47	right frontoparietal	partial	died	27.0
13.	male	63	right temporal	partial	died	26.0
14.	male	66	right temporal	partial	died	25.0
15.	male	54	left temporal	partial	died	24.0
16.	male	45	left parietooccipital	partial	died	20.0
17.	male	46	left occipital	partial	died	17.0
18.	female	52	left frontal	partial	died	14.0
19.	female	56	right frontal	partial	died	13.0
20.	male	53	left frontoparietal	partial	died	11.0

significantly better, as compared to the results from our previous cohorts, treated with rabies vaccine alone or a combination of Desferal and Cuprenil. In the present study, we did never observed side effects as a result of the treatment applied.

Discussion

Treatment of the glioblastoma multiforme is an extraordinary therapeutic problem. Surgery and optimal radiotherapy (60 Gy) alone prolong the patient's life to 11-15 months [1-4, 14. 15]. Some better results have been related to applying irradiation to 90 Gy [2, 10]. Nitrosourea drugs (CCNU, BCNU, ACNU) alone add 1-2 months, and temodal (temozolomide) adds 2.5 months to the postoperative survival of patients [4, 16-21].

Since 1981, we have used immunotherapy with rabies vaccine for the treatment of glioblastoma multiforme. The median postoperative survival of 20 patients reached 17.2 months by the end of October 1986 with three patients alive [12]. These patients survived two, four and six years after the operation, respectively.

Our further investigations revealed very interesting data, linked to the trace element aluminium. It was significantly augmented in the blood serum of the patients [22]. The content of the same element was twice as low in the tumors tissue removed intraoperatively, as compared to the quantity in the surrounding white brain matter [23]. The Ukrainian researchers O. Mykhaylyk et al. have found hyperferremia in human glial tumours [24], which is why we decided to use Desferal for chelation of iron and aluminium.

Cuprenil (D-penicillamine) has been applied for the treatment of experimental gliosarcoma in rats with definite success [25]. Previously, we had treated eight patients with glioblastomas multiforme, using large doses of Cuprenil (up to 3.75 g daily). This treatment in the last stage of the disease had no positive effect [26]. Cuprenil, however, suppresses tumour angiogenesis, which is typical for malignant tumours [27, 28]. That is the reason why we added it to combined therapy. The treatment of 21 patients with Desferal and Cuprenil yielded a final median postoperative survival of 20 months [13].

The present therapeutic study with rabies vaccine, Desferal and Cuprenil augmented the median postoperative survival to 28 months. Nearly half of the patients treated are alive

nowadays and the survival of the cohort is not a final one.

Conclusion

Adjuvant therapy of glioblastomas multiforme with rabies vaccine, Desferal and Cuprenil (D-penicillamine) has shown good efficacy and may be recommended for medical practice.

References

1. Miller PJ, Hassanein RS, Giri PGS. Univariate and multivariate statistical analysis of high-grade gliomas: the relationship of radiation dose and other prognostic factors. Int J Radiat Oncol Biol Phys. 1990;19(2):275-80.
2. Nwokedi EC, Dibiase SJ, Labbour S. Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. Neurosurgery. 2002;50(1):41-7.
3. Pigott TJD, Love JS, Palmer J. Statistical modeling in analysis of prognosis in glioblastoma multiforme: a study of clinical variables and Ki-67 index. Br J Neursosurg. 1991;5(1):61-6.
4. Stupp R, Mason WP, Van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med. 2005;352(10)987-96.
5. Davis C, Pandya P, Zawrence S. Intra-carotid cis-platinum for malignant glioma: is it worth it? Br J Neurosurg. 1991;5(4):424.
6. Nakagawa K, Kamezaki T, Shibata J. Effect of limfokine-activated killer cells with or without radiation therapy against malignant brain tumors. Neurol Med Chir (Tokyo). 1995;35(1):22-7.
7. Glantz MJ, Choy H, Kearns CM. Phase I study of weekly outpatient paclitaxel and concurrent cranial irradiation in adults with astrocytomas. J Clin Oncol. 1996;42(2):600-9.
8. Chanana AD, Capala J, Chadha M. Boron neutron capture therapy for glioblastoma multiforme. Neurosurgery.1999;44(6):1182-93.
9. Thomas DGT, Blechen NM, Roberts LT. MRC randomized trial of adjuvant chemotherapy in high grade glioma BR 05. Brit J Neurosurg. 1999;13(5):536.
10. Fitzek MM, Thornton AF, Rabinov JD. Accelerated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective Trial. J Neurosurg. 1999; 91(2):251-260.
11. Patel S, Breneman J, Warnick RE. Permanent iodine 125 interstitial implants for the treatment of recurrent glioblastoma multiforme. Neurosurgery. 2000;46(5):1123-30.
12. Philipov Ph. Attempt to use Rabies vaccine in the treatment of patients with glioblastoma multiforme. Vopr Neurochir. 1988;(3):38-40.
13. Philipov P. Trace elements selenium, manganese, copper and aluminium in patients with intracranial tumors concerning their therapeutic influence [dissertation]. Pleven: Medical University; 2004.
14. Fitzek MM, Thornton AF, Rabinov JD. Accelerated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective Trial. J Neurosurg. 1999; 91(2):251-260.
15. McGirt MJ, Chaichana KL, Gathinji M, Attenelo F, Than K, Jimenez A, Olivi A, Quinones Hinojosa A. Persistent outpatient hyperglycemia is independently associated with decreased survival after primary resection of malignant brain astrocytomas. Neurosurgery. 2008;63(2):286-91.
16. Ben-Hassell M, Gerduin D, Methlin A. Ajuvant postoperative modified (BCNU instead of CCNU) eight drugs in 1 day chemotherapy in adult patients with supratentorial malignant high grade glioma. Br J Neurosurg. 1996;10(1):117.
17. Fargeot P, Guignier F, Vogel C. Etude d'une association chirurgie-chimiotherapie lourde par BCNU avec autogreffe de moelle osseuse et radiotherapie dans les gliomes malins sus-tentoriels de l'adulte. Bull du Cancer. 1990;77(6):549-50.
18. Iwadate Y, Namba H, Sueyoshi K. Intra-arterial ACNU and cisplatinum chemotherapy for the treatment of glioblastoma multiforme. Neurol Med Chir (Tokyo). 1995;35(8):598-603.
19. Krauseneck P, Mertens HG, Messerer D, Kleihues P, Bamberg M, Dittmann W et al. German-Austrian study on malignant supratentorial gliomas. J Cancer Res Clin Oncol. 1986;111(Suppl 1):S9.
20. Pigott TJD, Love JS, Palmer J. Statistical modeling in analysis of prognosis in glioblastoma multiforme: a study of clinical variables and Ki-67 index. Br J Neursosurg. 1991;5(1):61-6.
21. Trojanowski T, Peszynski J, Turowski K. Quality of survival of patients with brain gliomas treated with post-operative CCNU and radiation therapy. J Neurosurg. 1989;70(1):18-23.
22. Philipov Ph, Tzachev K. Aluminium concentration in serum of patients with intracranial tumors. Zent bl Neurochir. 1993;54(1):148-50.
23. Philipov Ph, Tzachev K. Aluminium, manganese, copper and selenium in the neoplastic tissue and white brain matter of the patients with intracranial tumors. Proceedings of the 4th International symposium on trace elements in human; 2003 Oct. 9-11; Athens, Greece.2003. p. 430-4.
24. Mykhaylyk O, Dudchenko N, Cherchenko A. Peculiarities of nonheme iron metabolism upon glial brain tumors. Proceedings of the 3 rd International symposium on trace elements in

human; 2001 Oct 4-6; Athens, Greece. 2001. p. 1100-12.
25. Yoshida D, Ikeda Y, Nakazawa S. Suppression of tumor growth in experimental 9L gliosarcoma model by copper depletion. Neurol Med Chir (Tokyo). 1995;35(3):133-5.
26. Philipov Ph. A letter to the editor. Neurol Med Chir (Tokyo). 1996;36(2):115-6.
27. Brewer GJ, Merajver SD. Cancer therapy with Tetrathiomolybdate: Antiangiogenesis by lowering body copper a Review. Integr Cancer Ther. 2002;1(4):327-337.
28. Yoshida D, Ikeda Y, Nakazawa S. Copper chelation inhibits tumor angiogenesis in the experimental 9L gliosarcoma model. Neurosurgery. 1995;37(2):287-293.