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Overall Survival of Glioblastoma Patients Treated With a Combination of 7 Micronutrients: A Nutraceutical Trial

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Abstract

Background/Aim: There is increasing evidence for recognition of nutraceuticals as anti-tumour agents in various cancers. Over the years, anecdotal reports and our laboratory-based research have indicated their promising therapeutic potential for the management of glioblastoma. The aim of this study was to assess the effect of a combination of 7 micronutrients on overall survival of these patients.

Patients and Methods: A Nutraceutical study was conducted at King's College and St Thomas' Hospitals, London. Fifty-three newly diagnosed patients (37 males and 16 females) with glioblastoma were recruited consecutively in this randomised entry, double blind Phase II trial. The treatment (containing chokeberry extract, red grape seed extract, red clover extract, curcumin, selenium, tangeretin and lycopene) was given to two-thirds of the patients for 1 year after neurosurgery. This was consistent with the start date of their concomitant Stupp Protocol chemoradiation therapy. The patients in the placebo group had identical capsules which contained lactose only.

Results: Although the Kaplan – Meier analysis showed that the overall survival for the active and placebo groups was 14 and 13 months respectively, the results were not statistically significant (p=0.752).

Conclusion: This study has limitations but it acts as a proof of principle towards larger studies, as clearly sufficiently powered trials are crucial in determining the nature and size of the treatment effect. Future trials should consider subgroup analysis, with respect to such factors as patient's age at diagnosis, gender, extent of surgery, MGMT mutation and IDH status to identify the optimal responders.

Keywords*:* Glioblastoma multiforme, polyphenols, nutraceutical, micronutrients, Aronia melanocarpa, curcumin, tangeretin, selenium.

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Introduction

Glioblastomas (GBMs) constitute between 45 and 50 % of all malignant brain tumours in adults. They are the most common and aggressive subset of brain tumours classified by the World Health Organisation as grade 4 GBM (CNS5 WHO 2021) (1, 2). The mean incidence of these tumours in England has also been reported to increase in the last 2-3 decades (3). The current standard multi-modality treatment for newly diagnosed GBM patients is based on maximal safe surgical resection followed by concurrent chemoradiation with a DNA alkylating agent, temozolomide, followed by six months of adjuvant chemotherapy (4).

Although there have been recent advances in diagnosis, neurosurgery, radiotherapy and chemotherapy, the overall survival and quality of life for GBM patients remains dismal. Indeed, the median survival time has only improved slightly since the 2005 Stupp protocol from 14 months to approximately 16 months with a 5-year survival of less than 5% (5). Treatment remains a challenge due to the presence of the blood- brain barrier (BBB) which limits the concentration of drugs that can reach the tumour site. Other complex features of GBM include genomic and cellular heterogeneity (6). Glioma stem cells (GSCs) are a subpopulation of GBM cells which are capable of self-renewal and differentiation (7). The hallmarks of GBM such as unique tumour and immune microenvironment, proliferation, neoangiogenesis and induction of apoptosis render them resistant to chemoradiation therapy (8, 9). Additionally, the most significant biological feature of GBM which precludes successful therapy is infiltrative tumour cell invasion into the normal brain parenchyma. This results in tumour progression and recurrence which is the main cause of death of GBM patients (10).

GBM remains incurable. Hence there is a dire need for novel therapeutic intervention to improve survival and quality of life as well as offer renewed hope to these patients. Although reported recent clinical trial success of targeted therapies has been limited, there have been some promising results in developing neurosurgical approaches such as 5-aminolevulinic acid (5-ALA) guided resection (11), implanting Gliadel wafers containing chemotherapy at tumour site (12), anti-angiogenic therapies such as the monoclonal anti-VEGF-A antibody, bevacizumab (13), the use of electrical tumour-treating fields therapies as a non-invasive modality (14) and immunotherapies like dendritic cell vaccination (15).

Over the last 4 decades, a major research interest of our group has been glioma invasion. We proposed a strategy previously based on the therapeutic potential of a combination of micronutrients in the management of GBM: the "Nutraceutical Approach" (16). These dietary agents such as polyphenols are present abundantly in fruits, vegetables, nuts and tea. Polyphenols and their metabolites are reported to cross the blood brain barrier (17-19). Micronutrients are referred to as Nutraceuticals when used at pharmacological doses for therapy. Polyphenols are divided into flavonoids (e.g. flavones, anthocyanidins) and non-flavonoids (e.g. phenolic acid).

We screened various micronutrients to find a suitable combination (selenium, curcumin (from turmeric), *Aronia melanocarpa (*chokeberry extract), lycopene, red clover extract, red grape seed extract and tangeretin) to be tested in patients. Promising data from our lab-based research, on biopsy-derived cell cultures, have suggested that these micronutrients have differential anti-glioma potential: anti-invasive, pro-apoptotic and anti-angiogenic (20-24). This is in keeping with reports from other workers of increasing evidence that several micronutrients are now recognized as antitumour agents in GBM (25-27). This study aimed to assess the efficacy of a combination of 7 micronutrients on newly diagnosed GBM patients. The endpoint of this Nutraceutical trial was to determine if there was an improvement in overall survival.

Patients and Methods

Patients. Fifty-three patients were recruited for this randomized entry, double-blinded Phase II clinical trial using the TRial Randomiser (Borland Database Engine). They were divided into 2 groups: approximately two thirds (34 patients) were given active treatment and

nearly a third (19 patients) received a placebo. This study was approved by the local Ethical Committee of King's College Hospital (LREC no: 03-04-066). All the patients in this study underwent neurosurgery for GBM at the Department of Neurosurgery, King's College Hospital, London. They were recruited consecutively between 2009 and 2011 *via* co-ordination between the Neuro-oncologist, Specialist Nurses and Neurosurgical team.

The tumour samples were diagnosed histologically by a neuropathologist, according to the World Health Organisation (WHO) 2007 criteria (28). Almost halfway through the 2-year recruitment period, new molecular biology tests for prognostic markers were introduced in our Neuropathology labs for routine diagnosis of brain tumours. Since the methylation status of the O^6-methylguanine-DNA methyl-transferase (*MGMT*) gene promoter was recognized as an important biomarker of tumor response to temozolomide (29), MGMT promoter methylation assay (pyrosequencing) was henceforth used. The expression of isocitrate dehydrogenase (IDH1) and ATRX (a chromatin remodeler protein) antibodies using immunocytochemical assays were also included routinely.

The newly diagnosed GBM patients provided written informed consent and received identical standard therapies including surgery (biopsy or resection) followed by concurrent chemoradiation with temozolomide and then adjuvant chemotherapy for six months. Subsequently, they were followed up routinely, for as long as they survived, by the Neuro-oncology team at St Thomas' Hospital, London and Neurosurgical team at King's College Hospital, London.

Inclusion and exclusion criteria. To be eligible for recruitment, patients had to meet the following criteria: they had to be in the age range of 25–80 years with a newly diagnosed supratentorial GBM, histologically verified at the time of neurosurgery (biopsy or resection). They were also considered to be suitable for both radiotherapy and chemotherapy and had a Karnofsky performance score (KPS) of 70 or above. Patients were excluded from the study if they had a secondary or infratentorial GBM and a Karnofsky performance score of less than 70. Lactose intolerant patients were also in the exclusion criteria.

Study design and patient treatment. The study was designed to compare GBM patients who were given identical standard of care (neurosurgery followed by concomitant Chemoradiation therapy – Stupp protocol) as well as micronutrients or placebo. The micronutrients (also referred to as active treatment) was given as capsules to these patients after neurosurgery for 12 months. Patients in the placebo group had identical capsules containing lactose only for the same length of time.

The combination of the active treatment included 6 micronutrients (mostly polyphenols) blended and the total daily dose was divided to fit equally into 2 capsules based on the 12 hours bioavailability of red grape seed extract. This big capsule was taken by the patients twice a day. The seventh micronutrient, selenium, was in a separate small capsule and given once a day. Matching placebo capsules were prepared by Artemis International Inc, Indiana, USA and Cypress Systems, USA, respectively.

The purified combination of micronutrients included: 100 mg tangeretin (citrus methoxy flavone) purchased from Synergise, Canada; 90 mg genistein and 70 mg daidzein (isoflavones from red clover extract), donated by Linnea, Switzerland; 600 mg red grape seed extract (anthocyanidins), donated by Polyphenolics; 200 mg *Aronia melanocarpa* (anthocyanidins from chokeberry extract) donated by Artemis International Inc, Indiana, USA; 15 mg Lycopene (carotenoid) donated by LycoRed, Israel; 150 mg curcumin (carotenoid in turmeric) donated by Indo World Corporation, India and 200 µg selenium (trace element) donated by Cypress systems, USA. The chosen dosages were extrapolated from our *in vitro* studies on glioblastoma cells which were consistent with those recommended by each of our micronutrient supplier. The basic structures of the polyphenols used are shown in Figure 1.

Statistical analysis. The main endpoint of this trial was overall survival (OS) which was calculated from the first

day of treatment, namely the day of neurosurgery to the date of death for each patient. The OS rates and median survival times were estimated using the Kaplan-Meier method (30). All statistical analysis including overall survival statistics and Cox regression were performed using GraphPad Prism software (ver.10.3.1). The analysis aimed to elucidate any significant differences in OS between the active treatment and placebo groups.

Results

Patient characteristics. The main clinical data for the patients in the study are presented in Table I (active treatment) and II (placebo). These include histological classification, neurosurgical procedure, anatomical site of the tumour and the IDH1 and MGMT methylation status, if determined at the time. Fifty-three GBM patients (38 males and 15 females) were recruited. Their mean age was 57, ranging from 26-78 years. There were 2 young patients (aged 26 and 30), 11 patients were in their 40s, 18 in their 50s, 14 in their 60s and 8 in their 70s. They were followed up routinely as long as they were alive. Five patients withdrew from the study, 3 from the active group (aged 30, 53 and 63) and 2 from the placebo group (aged 46 and 75), at different times for various reasons, such as having difficulty swallowing large capsules, disease progression etc. The time of withdrawal from the trial was either close to the date of death (2 patients in the active group and 1 patient in the placebo group) or near the end of 1 year treatment (1 patient in the active group and 1 in the placebo group). As they were not lost to follow up, all 5 patients were included in the statistical analysis for overall survival. This did not obscure the data.

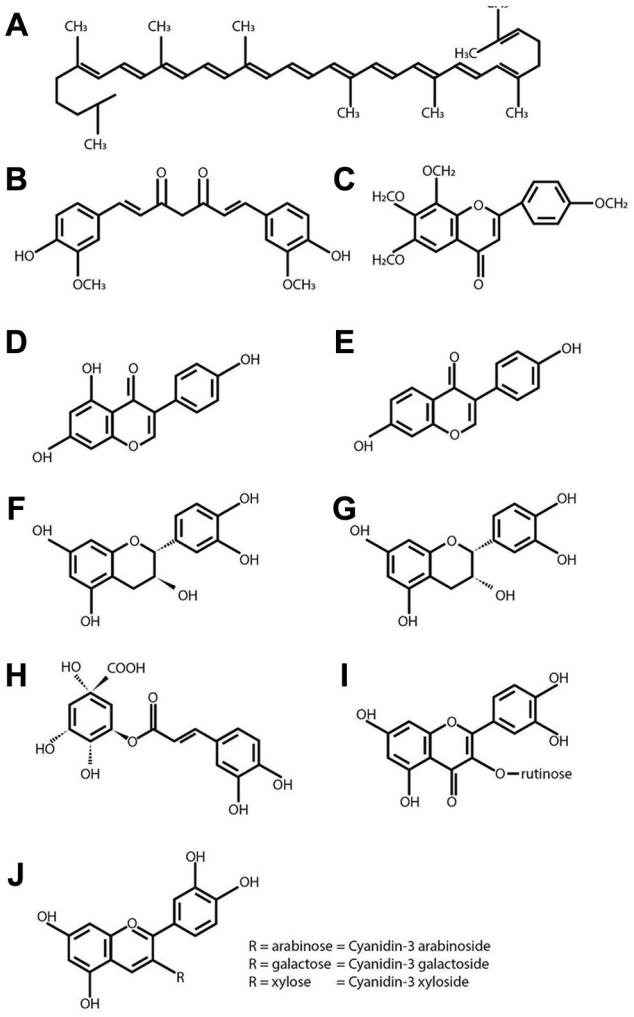

Figure 1. *Basic chemical structures of polyphenols used in this study. (A) Lycopene, (B) Curcumin, (C) Tangeretin, (D) Genistein, (E) Daidzein, (F) Catechin, (G) Epicatechin, (H) Chlorogenic acid (I) Rutin (J) various Anthocyanins.*

Overall survival. In this study, we compared overall survival of GBM patients in the active treatment and placebo groups using Kaplan-Meier curves (Figure 2). Survival analysis was done using the Cox regression model. Baseline comparisons were also made using Fisher's Exact test for the 2 groups in terms of age and gender and showed no difference (p=0.752). The median survival times for the active and placebo groups were 14 and 13 months, respectively. Overall survival did not differ significantly between the two groups based on the log-rank (Mantel-Cox) test (p=0.687). These results, with a median survival difference of 1 month, underscore that within the scope of our study, the active treatment did not impart a discernible impact on overall survival compared to the placebo.

The Proportional Hazard (PH) assumption was tested as the 2 curves in Figure 2 appeared to cross using Schoenfeld residual plot methods for treatment, age and

Table I. *Patient characteristics including histological classification, surgical procedure, anatomical sites, IDH1 and MGMT methylation status of 34 patients (25 male and 9 female) given active treatment.*

ACTIVE TREATMENT							
Patient ID	Age	Gender	GBM type	Neurosurgical procedure	Anatomical site of GBM	IDH1	MGMT status
GB01	56	M	Giant cell variant	Biopsy	L parietal white matter	ND	ND
GB02	60	M	Fibrillary	Craniotomy	R fronto-parietal	ND	ND
GB03	72	M	NS	Craniotomy and debulking	R temporal	ND	ND
GB04	62	M	Fibrillary	Craniotomy and debulking	R frontal	ND	ND
GB09	57	M	NS	Craniotomy	L temporal	ND	ND
GB10	55	F	NS	Craniotomy	R frontal	ND	ND
GB11	58	M	NS	Craniotomy and debulking	R frontal	ND	ND
GB13	49	F	Small cell variant	Craniotomy and debulking	R fronto-parietal	-	81 % meth
GB15	52	F	NS	Biopsy	R frontal	ND	ND
GB16	42	M	NS	Craniotomy and debulking	L frontal	-	6% meth
GB17	78	M	NS	Biopsy	L parietal	ND	ND
GB19	55	M	Oligo diff	Craniotomy and debulking with additional Gliadel wafers	R temporal	ND	ND
GB20	49	F	NS	Craniotomy and debulking	R parietal and trigonal	ND	ND
GB21	48	M	NS	Craniotomy and debulking	R frontal	ND	ND
GB23	60	M	NS	Biopsy	R frontal	ND	ND
GB25	44	F	NS	Craniotomy	R fronto-parietal	+	ND
GB26	53	M	NS	Craniotomy and debulking	R frontal	-	ND
GB28	47	M	NS	Craniotomy and debulking	L parieto- occipital	ND	unmeth
GB29	60	M	NS	Biopsy	R amygdala and hippocampus	ND	ND
GB30	63	M	Oligo diff	Craniotomy and debulking	R parieto- occipital	-	-ve
GB32	73	M	NS	Craniotomy and debulking	R occipito-temporal	-	10% meth
GB33	63	M	NS	Craniotomy and debulking	R parieto- occipital	ND	10% meth
GB35	67	F	NS	Craniotomy and debulking	R frontal	-	10% meth
GB37	30	F	NS	Craniotomy and debulking	L frontal	-	60% meth
GB38	53	M	NS	Craniotomy	R fronto-parietal	-	10% meth
GB40	65	F	NS	Craniotomy and debulking	R temporal	-	10% meth
GB41	26	M	Oligo diff	Craniotomy and debulking	R temporal horn	-	unmeth
GB43	54	M	NS	Craniotomy and debulking with additional Gliadel wafers	L parietal	-	10% meth
GB45	63	M	NS	Craniotomy and debulking	R temporal	-	20% meth
GB48	55	M	NS	Craniotomy and debulking	R temporal	ND	30% meth
GB49	52	M	NS	Craniotomy and debulking	R parietal	ND	10% meth
GB51	48	M	NS	Craniotomy and debulking with additional Gliadel wafers	L parieto- occipital	-	2% meth
GB52	46	M	Oligo diff	Craniotomy and debulking with additional Gliadel wafers	L temporal	-	50% meth
GB53	63	F	NS	Unresected [CT scan only]	R fronto-parietal & temporal	ND	ND

M: Male; F: female; NS: not specified; L: left; R: right; ND: not determined; GBM: glioblastoma; With Oligo diff: GBM with oligo dendroglial differentiation; -: negative; +: positive; meth: methylated; unmeth: unmethylated.

gender with time. For the sample variables in this study, the PH assumption was not violated and the initial K-M analysis was valid. Cox regression analysis revealed no significant effect of the active group on hazard. Patients in the active group did not differ significantly from the placebo group (HR=0.95, 95% CI:0.52–1.76, p=0.86). The effect of the active group did not differ by gender (HR=0.88, 95% CI:0.37–1.88, p=0.75).

Table II. *Patient characteristics including histological classification, surgical procedure, anatomical sites, IDH1 and MGMT methylation status of 19 patients (13 male and 6 female) in the placebo group.*

PLACEBO							
Patient ID	Age	Gender	GBM type	Neurosurgical procedure	Anatomical site of GBM	IDH1	MGMT status
GB05	72	M	NS	Craniotomy and debulking	R temporo-occipital	ND	ND
GB06	61	F	NS	Craniotomy and debulking with additional Gliadel wafers	R occipital	ND	ND
GB07	60	F	NS	Craniotomy and debulking	L parietal	ND	ND
GB08	53	M	NS	Biopsy	L fronto-parietal	ND	ND
GB12	46	F	NS	Craniotomy and debulking with additional Gliadel wafers	L temporo-frontal	ND	ND
GB14	71	M	NS	Craniotomy and debulking	L parieto- occipital	ND	ND
GB18	63	M	NS	Biopsy and debulking	R frontal & R basal ganglia	ND	ND
GB22	75	F	NS	Biopsy	R occipital	ND	ND
GB24	71	M	NS	Craniotomy and debulking	L paramedian posterior fossa	ND	ND
GB27	58	M	NS	Craniotomy and debulking	R frontal	ND	ND
GB31	70	F	NS	Craniotomy and debulking	R parietal	-	-
GB34	54	M	NS	Craniotomy and debulking	L temporal	-	ND
GB36	45	M	NS	Craniotomy and debulking	R frontal	-	10% meth
GB39	50	M	NS	Craniotomy and debulking with additional Gliadel wafers	L superior parietal	-	-
GB42	54	M	NS	Craniotomy and debulking with additional Gliadel wafers	L parieto- occipital	-	-
GB44	56	F	NS	Biopsy	L parietal	ND	ND
GB46	55	M	NS	Biopsy	Corpus callosum	ND	ND
GB47	49	M	NS	Craniotomy and debulking with additional Gliadel wafers	R temporal -parietal	-	60% meth
GB50	68	M	Oligo diff	Craniotomy and debulking	L temporal	-	40% meth

M: Male; F: female; NS: not specified; L: left; R: Right; ND: Not determined; GBM: Glioblastoma; With Oligo diff: GBM with oligo dendroglial differentiation; -: negative; meth: methylated; unmeth: unmethylated.

Discussion

Overall survival rates for patients with the aggressive primary brain tumour, GBM, at 5 years are reported to be 3-5%. This is due to GBM's high recurrence as well as resistance to the multi-modality approach used in conventional treatment. There has also been progress in the understanding of significant biological features of GBM which has led to clinical trials using targeted therapies (11-15).

Nonetheless, there is no notable improvement in overall survival despite advances in technologies and various therapeutic interventions over the last 4 decades. GBM has a dismal prognosis and remains incurable. Hence there is a dire need for novel therapeutic intervention to improve overall survival of these patients. Our group has been researching glioma invasion over the years and investigated the therapeutic potential of a number of micronutrients in the management of GBM (16).

Understandably, increasing numbers of GBM patients are seeking Complementary and Alternative Medicine (CAM) to alleviate standard therapy related toxicities and thereby improve prognosis. These include naturally occurring products like curcumin. Cannabis and its derivatives are also of interest to GBM patients. Preclinical data suggests that nabiximols (trade name Sativex) which are phytocannabinoids occurring naturally in cannabis plants, may have antitumour effects against GBM. A phase I clinical trial for safety and preliminary efficacy of nabiximols in recurrent GBM has been promising and also shown no drug interaction with temozolomide (31). A phase II clinical trial assessing temozolomide with or

without nabiximols in recurrent GBM (ARISTOCRAT) is ongoing and expected to expand to phase III later (32).

To the best of our knowledge, the Nutraceutical trial is the first Phase II double-blinded clinical trial using a combination of 7 micronutrients (selenium, tangeretin, lycopene, red grape seed extract, red clover extract, chokeberry extract and curcumin) for treating newly diagnosed GBM patients. The trial aimed to use this combination of non-toxic naturally occurring products which had been researched pre clinically by our group with promising results as well as anecdotal reports. A synergistic effect on overall survival in the clinical trial was anticipated. Some effects of these micronutrients are mediated by the modulation of intracellular signalling mechanisms related to biological features such as brain tumour invasion, apoptosis, angiogenesis and proliferation.

In contrast, of the above, only curcumin has been well documented for its ability to induce multiple cytotoxic effects in GBM including apoptosis, cell cycle arrest and disruption of molecular signaling (33). It has been shown by other workers to be a promising compound in clinical trials for various cancers including brain tumours (34-36). There was only a slight improvement in medial survival in our patients on micronutrients (14 *vs.* 13 months) compared to those on placebo, albeit non-statistically significant. No side effects were reported by any of the patients which is promising.

This study started in 2009 and the overall survival times for our placebo group are comparable to the findings of another study by deSouza *et al.* from our own Neuro-oncology Centre (King's College and St Thomas's Hospitals) in which survival analysis was compared in patients in years 1999-2000 and 2009-2010 (37). The overall survival had increased over the years in our unit due to strategies practiced in a multidisciplinary setting.

Nonetheless, there are limitations of this study which include a number of considerations. Firstly, there were changes introduced to routine diagnosis of brain tumours in our Neuropathology labs in 2010 after half the patients had been recruited. This included

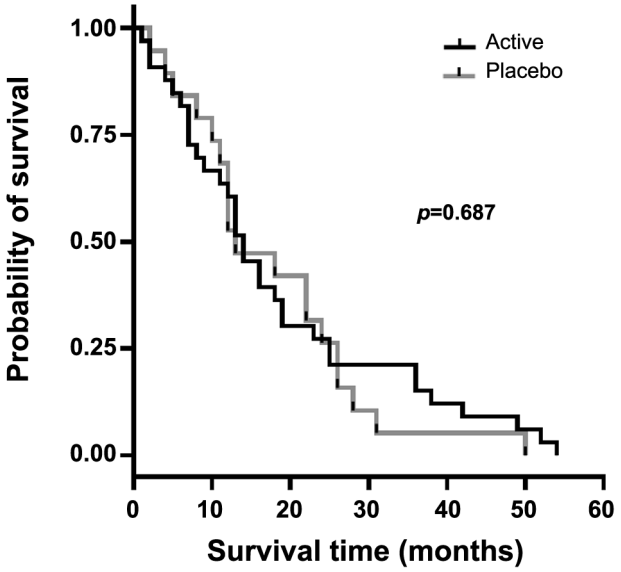

Figure 2. *Kaplan-Meier survival curves comparing overall survival for 53 newly diagnosed GBM patients with active group (black lines) and the placebo group (grey lines). The median survival times were 14 months for the active group and 13 months for the placebo group (95%CI=0.6124%). Log-Rank test, p=0.687, suggesting a non-statistically advantage for the active group. GBM: Glioblastoma.*

MGMT promoter methylation assay (pyrosequencing, a new molecular biology test for prognostic marker of tumor response to temozolomide (29). In addition, the expression of isocitrate dehydrogenase (IDH1) and ATRX (a chromatin remodeler protein) antibodies using immunocytochemical assays were also done routinely. Unfortunately, it was not possible to obtain an analysis of MGMT methylation status for 17 patients in the active group and 13 patients in the placebo group for reclassification purposes. These patients had been recruited prior to the introduction of these diagnostic changes in our labs. Similarly, IDH1 was not determined for 19 patients in the active group and 12 patients in the placebo group (Table I and II).

The tumour samples were diagnosed histologically according to the 2007 WHO criteria for this study. It would be interesting to see what impact could have been made on the statistics with the more recent 2016 WHO classification of tumours of the CNS which added molecular / gene mutation criteria to the diagnostic

classification (38). However, the European Association for Neuro-Oncology (EANO) reported in 2017 that this had little impact on patient improvement or molecular targeting on malignant gliomas (39).

Other limitations of this study which may have influenced the findings include the neurosurgical procedures in that although most of the 53 patients had craniotomy with debulking, there were 9 patients who had additional Gliadel wafers. Ten patients had biopsy and 1 patient had an unresected tumour (CT scan only). In addition, there were 8 patients who had neurosurgery twice and one of the youngest patients had surgery 4 times. Patients with biopsy only do not have as good a prognosis as those with craniotomy with debulking (40).

Conclusion

The combination of nutraceuticals used in this trial indicated a small improvement in the overall survival of GBM patients albeit not statistically significant. Sativex could also be used in combination with nutraceuticals. This study acts as a proof of principle towards the need for larger studies as clearly sufficiently powered trials are crucial in determining both the nature and size of the treatment effect. With recent changes in classification of brain tumours, future trials should also allow subgroup analysis, with respect to such factors as patient's age at diagnosis, gender, MGMT mutation status and LDH wild type. Other factors for consideration include Karnofsky Performance Status, tumour site, craniotomy and debulking instead of biopsy only to identify the optimal responders.

Conflicts of Interest

No conflict of interest was declared by any of the authors.

Author's Contributions

HKR, RB, GJP and RWG designed the study. KA and RWG provided the surgical material. RB, KA and HKR recruited patients. RWG, HKR and RB contributed to following up patients. PL analyzed the data. HKR, GJP, RWG and PL contributed to writing the paper. GJP and KA proofread the manuscript. HKR and GJP edited it. All authors read and approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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